Sonrotoclax + zanubrutinib for TN-CLL demonstrates MRD clearance and tolerability in ongoing phase 1/1b (BGB-11417-101)

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ABSTRACT

Introduction: BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, phase 1/1b dose-escalation/expansion study in patients with B-cell malignancies. Updated safety and efficacy of sonrotoclax (BGB-11417) + zanubrutinib in treatment-naive (TN)-CLL/SLL are presented.

Methods: Patients received zanubrutinib (320 mg once daily [QD] or 160 mg twice daily) for 8-12 weeks, then added sonrotoclax via ramp-up (160 or 320 mg QD). Endpoints included safety, ORR (iwCLL), and minimal residual disease in blood per modified ERIC flow panel (uMRD4).

Results: As of 10May2024, 112 patients were enrolled (high TLS risk, 34%; unmutated IGHV, 51%; *TP53* mutation, 20%; del(17p), 9%). Median follow-up was 18.3 months (range, 4.4-29.9). The most common TEAEs were neutropenia (41%), contusion (38%), COVID-19 (30%), and diarrhea (29%). Neutropenia was the most common grade ≥3 TEAE (26%); 2 patients had a dose reduction/hold, and none discontinued treatment. Two patients (160 mg) had grade 3 febrile neutropenia. No TLS or deaths occurred. Five patients (160 mg) discontinued combination treatment: TEAE, PD, patient withdrawal (n=1 each), elective discontinuation after 96 weeks of treatment (n=2); 1 patient (320 mg) discontinued zanubrutinib only due to intermittent grade 1 diarrhea. In 108 evaluable patients, ORR was 100% (CR: 160 mg, 41%; 320 mg, 42%). Median time to response was 2.6 months (range, 1.5-10.8); median time to CR was 8.4 months (range, 3.9-17.1). Week 24/48 best blood uMRD4 rates were 61%/79% (sonrotoclax 160 mg) and 77%/90% (sonrotoclax 320 mg). Median time to uMRD was 9.7 months (range, 3.9-20.6) with 160 mg and 8.5 months (range, 5.4-19.9) with 320 mg. No progression was seen in the sonrotoclax 320 mg cohort.

Conclusion: Sonrotoclax + zanubrutinib was well tolerated in patients with TN-CLL/SLL. Substantial efficacy was observed, with 100% ORR in assessed patients and 90% best uMRD rate in the 320 mg cohort patients who reached 48 weeks of therapy. High blood uMRD4 rates occurred early and were sustained. A registrational phase 3 study (CELESTIAL-TNCLL; BGB-11417-301) assessing this combination with sonrotoclax 320 mg is recruiting.