Sonrotoclax monotherapy for treatment of patients with relapsed/refractory CLL: data from an ongoing phase 1/1b study (BGB-11417-101)

Authors: Stephen S. Opat,[1] Emma Verner,[2,3] Masa Lasica,[4] Mary Ann Anderson,[5,6] Tamara Marconi,[7] Almudena Navarro-Bailón,[8] Paolo Ghia,[9,10] Monica Tani,[11] Shuo Ma,[12] David Bond,[13] Yiqian Fang,[14] James Hilger,[15] Sheel Patel,[15] Nicole Lamanna[16]

Affiliations: [1]Lymphoma Research Group, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia; [2]Concord Repatriation General Hospital, Concord, NSW, Australia; [3]University of Sydney, Sydney, NSW, Australia; [4]St Vincent's Hospital Melbourne, Melbourne, VIC, Australia; [5]Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [6]The Walter and Eliza Hall Institute, Melbourne, VIC, Australia; [7]Box Hill Hospital, Box Hill, VIC, Australia; [8]Hospital Universitario de Salamanca, Salamanca, Spain; [9]Università Vita-Salute San Raffaele, Milano, Italy; [10]IRCCS Ospedale San Raffaele, Milano, Italy; [11]Santa Maria delle Croci Hospital, Ravenna, Italy; [12]Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [13]The James Cancer Hospital and Solove Research Institute at the Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; [14]BeOne Medicines Ltd, Shanghai, China; [15]BeOne Medicines Ltd, San Carlos, CA, USA; [16]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY, USA

ABSTRACT

Objective: B-cell lymphoma 2 (BCL2) inhibition is an established treatment strategy in chronic lymphocytic leukemia/small lymphocytic lymphoma (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). Here, safety, tolerability, and efficacy data of sonrotoclax monotherapy in patients with relapsed/refractory (R/R) CLL/SLL without a history of prior venetoclax treatment are presented.

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 Common Terminology Criteria for Adverse Events v5.0. Secondary endpoints included establishing the maximum tolerated dose (MTD), recommended phase 2 dose, and overall response rate (ORR) per International Workshop on CLL 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 years (range, 55-84 years); 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 months (range, 2.6-47.7 months); 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

hours 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.

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.