**Updated efficacy and safety of the bruton tyrosine kinase degrader BGB-16673 in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: results from the ongoing phase 1 CaDAnCe-101 study**

**Authors:** Stephan Stilgenbauer,[1] Lydia Scarfò,[2,3] Ricardo D. Parrondo,[4] Meghan C. Thompson,[5] Anna Maria Frustaci,[6] John N. Allan,[7] Paolo Ghia,[2,3] Irina Mocanu,[8] Constantine S. Tam,[9] Damien Roos-Weil,[10] Judith Trotman,[11] Inhye E. Ahn,[12] Nicole Lamanna,[13] Linlin Xu,[14] Kunthel By,[14] Shannon Fabre,[14] Daniel Persky,[14] Amit Agarwal,[14] John F. Seymour[15]

**Affiliations:** [1]Ulm University, Ulm, Germany; [2]Università Vita-Salute San Raffaele, Milano, Italy; [3]IRCCS Ospedale San Raffaele, Milano, Italy; [4]Mayo Clinic - Jacksonville, Jacksonville, FL, USA; [5]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [7]Weill Cornell Medicine, New York, NY, USA; [8]Institute of Oncology, ARENSIA Exploratory Medicine, Düsseldorf, Germany; [9]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [10]Pitié-Salpêtrière Hospital, Paris, France; [11]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [12]Dana-Farber Cancer Institute, Boston, MA, USA; [13]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY, USA; [14]BeOne Medicines Ltd, San Carlos, CA, USA; [15]Peter MacCallum Cancer Centre, Royal Melbourne Hospital, and University of Melbourne, Melbourne, VIC, Australia

## ABSTRACT

**Background:** Bruton tyrosine kinase (BTK) inhibitors are effective treatments for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), but intolerance and/or acquired resistance due to BTK mutations can emerge. BGB-16673 is a protein degrader that blocks BTK signalling by tagging BTK for degradation through the cell's proteasome pathway.

**Methods:** Eligible patients must have confirmed R/R CLL/SLL (≥2 prior therapies), an Eastern Cooperative Oncology Group performance status of 0-2, and adequate organ function. In the US/EU/Australia, patients must have previously received a covalent BTK inhibitor (cBTKi). BGB-16673 was dosed once daily orally. Primary objectives were to assess safety/tolerability (CTCAE v5.0; iwCLL hematologic toxicity criteria) and establish the maximum tolerated dose and recommended dose for expansion. A secondary objective was to assess overall response rate (ORR) (iwCLL 2018 criteria with partial response with lymphocytosis [PR-L] modification; 2014 Lugano criteria for SLL).

**Results:** As of December 17, 2024, 66 patients with CLL/SLL were enrolled and treated (50 mg, n=1; 100 mg, n=22; 200 mg, n=16; 350 mg, n=15; 500 mg, n=12). Median age was 70

(range 47-91) years; the median number of prior therapies was 4 (range, 2-10), including prior cBTKis (n=61; 92.4%), BCL2 inhibitors (BCL2is; n=54; 81.8%), and noncovalent BTKis (ncBTKis; n=14;21.2%). In total, 65.2% (43/66) of patients had del(17p) and/or *TP53* mutation and 79.6% (39/49) had unmutated IGHV. Median follow-up was 13.1 (range, 0.3-29.9) months.
Overall, 92.4% of patients had any-grade treatment-emergent adverse events (TEAEs; grade ≥3, 51.5%); those in ≥30% of patients were fatigue (36.4%; grade ≥3, 1.5%) and contusion/bruising (30.3%; no grade ≥3). Grade ≥3 TEAEs in ≥10% of patients were neutropenia/neutrophil count decreased (21.2%) and pneumonia (12.1%). Atrial fibrillation (grade 1 in the context of bacterial pneumonia) and febrile neutropenia (in the context of COVID-19 pneumonia and norovirus diarrhea) occurred in 1 pt (1.5%) each. Hypertension (n=2, both grade 3) and major hemorrhage occurred in 2 patients each (3.0%, grade 1 subarachnoid hemorrhage resolved; grade 3 subdural hemorrhage outcome unknown). Six patients (9.1%) had a TEAE leading to dose reduction. Four patients had TEAEs that led to death (pneumonia in the context of disease progression, septic shock, bronchopulmonary and cerebral aspergillosis, and acute respiratory failure; n=1 each); no deaths were deemed related to BGB-16673.

In 66 response-evaluable patients, ORR (PR-L or better) was 80.3% (n=53), and complete response (CR)/CR with incomplete recovery (CRi) rate was 3.0% (n=2). At 200 mg, ORR was 93.8% (15/16), including 1 CR. Median time to first response was 2.8 (range, 2.0-10.9) months. Thirty-three patients (50.0%) remained on treatment for ≥12 months; 38 patients had ongoing responses. Responses deepened over time: of 19 patients with initial PR-L, 10 transitioned to partial response (PR) and 1 to CR; of 15 patients with initial stable disease, 1 transitioned to PR-L, 5 to PR, and 1 to CRi. Responses were seen at the lowest dose (50 mg, 1/1); in patients previously treated with a cBTKi (49/61; 80.3%) or ncBTKi (10/14; 71.4%) and with double- (cBTKi and BCL2i; 36/41; 87.8%) and triple-exposure (cBTKi, BCL2i, ncBTKi; 9/12; 75.0%); and in patients with (17/24; 70.8%) and without (33/39; 84.6%) *BTK* mutations, and with del(17p) and/or *TP53* mutation (33/43; 76.7%). Median progression-free survival was not reached.

**Summary/Conclusion:** Data from this ongoing study demonstrate that the novel BTK degrader BGB-16673 has a tolerable safety profile and shows robust and deepening responses in patients with heavily pretreated R/R CLL/SLL, including those with prior BTKi treatment and BTKi mutations.