BGB-16673, a Bruton tyrosine kinase (BTK) degrader, in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): a phase 1 CaDAnCe-101 study update

Authors: Stephan Stilgenbauer,[1] Ricardo D. Parrondo,[2] Meghan C. Thompson,[3] Anna Maria Frustaci,[4] John N. Allan,[5] Paolo Ghia,[6,7] Irina Mocanu,[8] Damien Roos-Weil,[9] Constantine S. Tam,[10] Judith Trotman,[11] Inhye E. Ahn,[12] Lydia Scarfò,[6,7] Carlo Visco,[13] Michael Choi,[14] Yanan Zhang,[15] Linlin Xu,[15] Kunthel By,[15] Shannon Fabre,[15] Daniel Persky,[15] Shelonitda Rose,[15] John F. Seymour[16]

Affiliations: [1]Ulm University, Ulm, Germany; [2]Mayo Clinic - Jacksonville, Jacksonville, FL, USA; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [5]Weill Cornell Medicine, New York, NY, USA; [6]Università Vita-Salute San Raffaele, Milano, Italy; [7]Comprehensive Cancer Center, IRCCS Ospedale San Raffaele, Milano, Italy; [8]The Institute of Oncology, ARENSIA Exploratory Medicine, Chisinau, Moldova; [9]Pitié-Salpêtrière Hospital, Paris, France; [10]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [11]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [12]Dana-Farber Cancer Institute, Boston, MA, USA; [13]Universita di Verona, Verona, Italy; [14]Moores Cancer Center, University of California San Diego, La Jolla, CA, USA; [15]BeOne Medicines Ltd, San Carlos, CA, USA; [16]Peter MacCallum Cancer Centre, Royal Melbourne Hospital, and University of Melbourne, Melbourne, VIC, Australia

Background: BTK inhibitors (BTKis) are effective treatments (tx) for CLL/SLL; however, development of resistance and intolerance remain a challenge. BGB-16673 is a BTK degrader that blocks signaling by tagging BTK for degradation through the cell's proteasome pathway, leading to tumor regression. The ongoing open-label, phase 1/2 CaDAnCe-101 (BGB-16673-101; NCT05006716) study is evaluating BGB-16673 monotherapy in patients (pts) with B-cell malignancies.

Aims: To report updated safety and efficacy results for phase 1 of the CaDAnCe-101 trial in pts with R/R CLL/SLL.

Methods: Eligible pts had a diagnosis of R/R CLL/SLL (≥2 prior therapies), an ECOG performance status of 0-2 (0-1 in the EU), and adequate organ function. Pts in the US, EU, and Australia must have received prior tx with a covalent BTKi. BGB-16673 was administered orally once daily. The primary phase 1 study objectives were to assess safety/tolerability (NCI-CTCAE v5.0; iwCLL hematologic toxicity criteria) and to establish the maximum tolerated dose and recommended expansion dose. Secondary objectives included assessing the overall response rate (ORR) per iwCLL 2018 criteria with the partial response (PR) with lymphocytosis (PR-L) modification and per the 2014 Lugano criteria (SLL), with the first assessment after 12 weeks of tx.

Results: As of the Dec 15, 2025, data cutoff, 67 pts with R/R CLL/SLL received BGB-16673 (50 mg, n=1; 100 mg, n=22; 200 mg, n=17; 350 mg, n=15; 500 mg, n=12).

Median age was 70 (range, 47-91) years, and pts received a median of 4 prior lines of therapy (range, 2-10). Prior therapies included covalent BTKis (n=63 [94.0%]), noncovalent BTKis (n=14 [20.9%]), and BCL2 inhibitors (n=55 [82.1%]). Baseline mutations are shown (Table). Median study follow-up was 24.1 (range, 0.3-37.7) months, and 35 pts (52.2%) remained on tx at data cutoff.

Any-grade tx-emergent adverse events (TEAEs) occurred in 97.0% of the 67 pts; TEAEs in ≥25% of pts were fatigue (37.3%), contusion (32.8%), diarrhea (29.9%), and neutropenia/neutrophil count decreased (29.9%). Grade ≥3 TEAEs occurred in 61.2% of pts; those occurring in ≥5% were infections (34.3%), neutropenia/neutrophil count decreased (25.4%), and thrombocytopenia/platelet count decreased (7.5%). TEAEs led to dose reduction in 9 pts (13.4%) and tx discontinuation in 12 pts (17.9%), 4 (6.0%) of whom had tx-related TEAEs (subdural hemorrhage, peripheral swelling and ecchymosis, maculopapular rash, and disseminated aspergillosis). Among 67 pts, 5 (7.5%) had TEAEs that led to death (all due to infection; one in the context of progressive disease [PD]).

Among all 67 pts, the ORR (≥PR-L) was 85.1% (n=57), and the PR or better rate was 77.6% (n=52); the complete response (CR)/CR with incomplete marrow recovery rate (CRi) was 3.0% (n=2). At the 200-mg dose, the ORR was 94.1% (16/17), with 1 CR. Median time to first response was 2.8 (range, 2.0-19.4) months, and median duration of response was 20.7 (range, 0-27.6) months. Responses were seen in pts with high-risk features (Table); responses by BTKi/BCL2i refractoriness will be presented. The 18-month PFS rate was 65.2% (95% CI, 50.9%-76.2%); 21 pts (31.3%) had PD, and 5 (7.5%) died.

Summary/Conclusion: These data demonstrate that the novel BTK degrader BGB-16673 continues to have a manageable safety profile with durable responses in pts with R/R CLL/SLL, including in pts with difficult-to-treat CLL/SLL. BGB-16673 (200 mg) is being evaluated in ongoing phase 2 and 3 studies in pts with R/R CLL/SLL.

Table. ORR (defined as PR-L or better) according to prior therapy and mutation status

Characteristic	Patients, n/N (%)	ORR, n/N (%)
Prior therapy		
cBTKi and BCL2i	43/67 (64.2)	40/43 (93.0)
cBTKi, BCL2i, and ncBTKi	12/67 (17.9)	9/12 (75.0)
Mutation status		
BTK mutation	25/66 (37.9)	19/25 (76.0)
del(17p)/*TP53* mutation	44/67 (65.7)	35/44 (79.5)
PLCG2 mutation	10/66 (15.2)	9/10 (90.0)
IGHV unmutated	37/48 (77.1)	32/37 (86.5)
Complex karyotype (≥3 abnormalities)	23/43 (53.5)	17/23 (73.9)

BCL2i, B-cell lymphoma 2 inhibitor; BTK, Bruton tyrosine kinase; cBTKi, covalent BTK inhibitor; IGHV, immunoglobulin heavy-chain variable region; ncBTKi, noncovalent BTK inhibitor; PR-L, partial response with lymphocytosis.