BGB-16673, a Bruton tyrosine kinase (BTK) degrader, in patients with relapsed/refractory (R/R) Waldenström macroglobulinemia (WM): a phase 1 CaDAnCe-101 study update

Authors: Judith Trotman,[1] Chan Y. Cheah,[2-4] John F. Seymour,[5] Constantine S. Tam,[6] Ricardo D. Parrondo,[7] Anna Maria Frustaci,[8] Damien Roos-Weil,[9] Eugen Tausch,[10] Anne-Sophie Michallet,[11] Georg Hess,[12] Franziska Bach,[13] Herbert Eradat,[14] Yanan Zhang,[15] Linlin Xu,[15] Kaiyuan Hua,[15] Shannon Fabre,[15] Motohisa Takai,[15] Shelonitda Rose,[15] Mazyar Shadman[16,17]

Affiliations: [1]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [2]Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [3]Medical School, University of Western Australia, Crawley, WA, Australia; [4]Linear Clinical Research, Nedlands, WA, Australia; [5]Peter MacCallum Cancer Centre, Royal Melbourne Hospital, and University of Melbourne, Melbourne, VIC, Australia; [6]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [7]Mayo Clinic - Jacksonville, Jacksonville, FL, USA; [8]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [9]Pitié-Salpêtrière Hospital, Paris, France; [10]Ulm University, Ulm, Germany; [11]Centre Léon Bérard, Lyon, France; [12]Department of Hematology and Medical Oncology, University Medical School Mainz, Mainz, Germany; [13]University of Cologne, Center for Integrated Oncology Aachen Bonn Köln Düsseldorf, Cologne, Germany; [14]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [15]BeOne Medicines, Ltd, San Carlos, CA, USA; [16]Fred Hutchinson Cancer Center, Seattle, WA, USA; [17]University of Washington, Seattle, WA, USA

Background: 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 of BGB-16673 in pts with R/R WM in the phase 1 portion of CaDAnCe-101.

Methods: Eligible pts had confirmed R/R WM (≥2 prior therapies); an ECOG performance status of 0-2 (0/1 in the EU); and previous treatment (tx) with an anti-CD20 antibody and a covalent BTK inhibitor (BTKi). BGB-16673 was administered orally once daily. The primary objectives were to determine the safety/tolerability (NCI-CTCAE v5.0), maximum tolerated dose, and recommended dose for expansion. A key secondary objective was the overall response rate (ORR, defined as ≥minor response; IWWM-11 consensus criteria); the major response rate (MRR) was defined as ≥partial response.

Results: As of the Dec 15, 2025, data cutoff, 43 pts with R/R WM received BGB-16673 (100 mg, n=15; 200 mg, n=15; 350 mg, n=13). Median age was 72 (range, 46-81) years, and median number of prior therapies was 3 (range, 2-11). Prior therapies included an anti-CD20 antibody (n=43 [100%]), covalent BTKi (n=43 [100%]),

noncovalent BTKi (n=7 [16.3%]), BCL2 inhibitor (n=10 [23.3%]), chemotherapy (n=40 [93.0%]), and proteasome inhibitor (n=14 [32.6%]); 36 pts (83.7%) discontinued prior BTKi due to progressive disease (PD). Baseline mutation status is shown (Table). Median study follow-up was 14.3 (range, 0.2-37.3) months. At data cutoff, 26 pts (60.5%) remained on tx; of the 17 pts who discontinued, the primary reason for discontinuation was PD in 6 pts (35.3%).

Overall, 95.3% of pts experienced any-grade tx-emergent adverse events (TEAEs; grade ≥3, 60.5%). The most common any-grade TEAEs in ≥25% of pts were neutropenia/neutrophil count decreased (37.2%), diarrhea (30.2%), and contusion (27.9%). Grade ≥3 TEAEs in ≥10% of pts included neutropenia/neutrophil count decreased (34.9%) and anemia (14.0%). Eight pts (18.6%) had a grade ≥3 infection. No atrial fibrillation occurred. Febrile neutropenia and major hemorrhage (grade 3 hematemesis) occurred in 1 pt (2.3%) each. Five pts (11.6%) had TEAEs that led to tx discontinuation, and 3 (7.0%) pts had TEAEs that led to dose reduction. As previously reported, 3 pts (7.0%) died due to TEAEs.

Among the 42 response-evaluable pts, the ORR was 85.7% (n=36), the MRR was 76.2% (n=32), and the very good partial response rate was 31.0% (n=13). Median time to first overall response was 1.0 (range, 0.9-8.2) months and to best overall response was 2.8 (range, 1.0-12.2) months. Responses were also observed in pts with high-risk features, including *BTK* mutations (Table), and in 29/35 pts (82.9%) who discontinued a prior BTKi due to PD. After a progression-free survival (PFS) median follow-up of 16.6 (95% CI, 13.8-19.5) months, the estimated 15-month PFS rate was 70.4% (95% CI, 52.6%-82.5%).

Summary/Conclusion: These phase 1 data from the CaDAnCe-101 study demonstrate that the novel BTK degrader BGB-16673 has a manageable safety profile with substantial antitumor activity in heavily pretreated pts with R/R WM, including pts with WM bearing *BTK*, *CXCR4*, and *TP53* mutations. Responses deepened over time, with early evidence of response durability. The phase 2 portion of the study is actively enrolling.

Table. Response rate by mutation status

Mutation status[a]	Patients, n/N (%)	ORR, n/N (%)	MRR, n/N (%)
BTK mutated	13/42 (31.0)	13/13 (100)	13/13 (100)
MYD88 mutated	33/42 (78.6)	29/33 (87.9)	25/33 (75.8)
CXCR4 mutated	19/42 (45.2)	19/19 (100)	16/19 (84.2)
TP53 mutated	23/42 (54.8)	21/23 (91.3)	20/23 (87.0)
PLCG2 mutated	3/42 (7.1)	3/3 (100)	2/3 (66.7)

[a]Mutation status was unknown in 1 patient.
BTK, Bruton tyrosine kinase; ORR, overall response rate (≥minor response); MRR, major response rate (≥partial response).