

Updated efficacy and safety results of the Bruton tyrosine kinase degrader BGB-16673 in patients with relapsed/refractory Waldenström macroglobulinemia from the ongoing phase 1 CaDAnCe-101 study

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Introduction: BGB-16673 is an orally available protein degrader that blocks BTK signaling by tagging BTK for degradation through the cell's proteasome pathway, leading to tumor regression. CaDAnCe-101 (BGB-16673-101; NCT05006716) is an ongoing open-label, phase 1/2 study evaluating BGB-16673 monotherapy in patients with B-cell malignancies. Here, updated safety and efficacy results of BGB-16673 are presented in patients with WM in the phase 1 portion of the study.

Methods: Eligible patients had confirmed relapsed/refractory (R/R) WM (≥ 2 prior therapies), an ECOG performance status of 0-2 (0-1 in the EU), and previous treatment with an anti-CD20 antibody and, in the US, Japan, and EU, a covalent BTK inhibitor. BGB-16673 was dosed once daily orally. The primary objectives of this phase 1 study were to evaluate safety and tolerability (NCI-CTCAE v5.0) and establish the maximum tolerated dose and recommended dose for expansion. A secondary objective was to evaluate the overall response rate (ORR; modified IWWM-6 consensus criteria), with the first assessment after 4 weeks of treatment.

Results: As of May 23, 2025, 42 patients with WM were enrolled and treated (100 mg, n=15; 200 mg, n=14; 350 mg, n=13). Median age was 72.0 years (range, 46-81 years), and the median number of prior therapies was 3 (range, 2-11), including prior covalent BTK inhibitors (n=42 [100%]), BCL2 inhibitors (n=10 [23.8%]), noncovalent BTK inhibitors (n=7 [16.7%]), anti-CD20 monoclonal antibodies (n=42 [100%]), and chemotherapy (n=39 [92.9%]). In total, 33.3% of patients (12/36) had WM with *BTK* mutations, 85.7% (36/42) with *MYD88* mutations, 51.3% (20/39) with *CXCR4* mutations,

52.8% (19/36) with *TP53* mutations, and 5.6% (2/36) with *PLCG2* mutations. Median follow-up was 8.8 months (range, 0.8-31.0 months).

Overall, 97.6% of patients experienced treatment-emergent adverse events (TEAEs) of any grade (grade ≥ 3 , 59.5%; serious TEAEs, 35.7%). The most common ($\geq 20\%$ incidence) TEAEs (any grade; grade ≥ 3) were neutropenia (38.1%; grade ≥ 3 , 33.3%, most common grade ≥ 3 TEAE), diarrhea (26.2%; no grade ≥ 3), contusion/bruising (26.2%; no grade ≥ 3), and thrombocytopenia (21.4%; grade ≥ 3 , 7.1%). No atrial fibrillation was observed. Grade 3 febrile neutropenia and major hemorrhage (grade 3 hematemesis caused by concurrent gastritis/duodenitis unrelated to treatment) occurred in 1 patient (2.4%) each. Seven patients (16.7%) had a grade ≥ 3 infection, including 2 patients with fungal infections. Three patients (7.1%) had TEAEs that led to treatment discontinuation (anemia, cerebral aspergillosis, pericardial effusion/pleural effusion; n=1 each), and 2 patients (4.8%) had a TEAE that led to dose reduction. Two patients (4.8%) died due to TEAEs (septic shock in the context of progressive disease [PD] and cerebral aspergillosis; n=1 each).

All 42 patients were response-evaluable and the ORR (minor response [MR] or better) was 83.3% (n=35), the major response rate (partial response [PR] or better) was 64.3% (n=27), and the very good partial response (VGPR) rate was 26.2% (n=11). Median time to first overall response was 1.0 months (range, 0.9-3.8 months) and to best overall response was 1.9 months (range, 0.9-7.4 months). Responses deepened over time: of 9 patients with stable disease at first disease assessment, 3 transitioned to MR and 2 to PR; of 20 patients with initial MR, 10 transitioned to PR and 2 to VGPR; and of 13 patients with initial PR, 7 transitioned to VGPR. Thirty patients (71.4%) remain on treatment. Two deaths were due to PD. Responses were seen in patients previously treated with a covalent BTK inhibitor (35/42 [83.3%]) and a noncovalent BTK inhibitor (7/7 [100%]) and in patients who discontinued a prior BTK inhibitor due to PD (28/35 [80%]). Responses were independent of mutations in *BTK* (with, 12/12; without, 17/24), *MYD88* (with, 30/36; without, 5/6), *CXCR4* (with, 18/20; without, 14/19), *TP53* (with, 16/19; without, 13/17), and *PLCG2* (with, 1/2; without, 28/34). The 9-month duration of response rate was 84.1% (95% CI, 63.1%-93.7%).

Conclusions: Data from this ongoing phase 1 study demonstrate that the novel BTK degrader BGB-16673 was well tolerated and continued to show substantial antitumor activity in patients with heavily pretreated BTK inhibitor–exposed R/R WM, including those with *BTK*, *MYD88*, *CXCR4*, and *TP53* mutations. Enrollment is ongoing in the phase 2 portion of the study.