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Tacabrutideg (BGB-16673), a Bruton tyrosine kinase (BTK) degrader, in patients with relapsed/refractory (R/R) Waldenström macroglobulinemia (WM): updated safety and efficacy data from the phase 1 CaDAnCe-101 study

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Introduction: BTK is a key mediator of signaling pathways involved in the pathogenesis of WM. Tacabrutideg (BGB-16673) is a potential first-in-class BTK degrader that induces BTK degradation through the proteasome pathway, leading to tumor regression. Here we report updated safety and efficacy results of tacabrutideg in

patients (pts) with R/R WM in phase 1 of the ongoing open-label, phase 1/2 CaDAnCe-101 study (BGB-16673-101; NCT05006716).

Methods: Eligible pts had confirmed R/R WM (≥2 prior therapies), an ECOG performance status of 0-2 (EU: 0/1), and prior treatment with an anti-CD20 antibody and covalent BTK inhibitor (BTKi). Tacabrutideg was administered orally once daily. Primary objectives were the safety/tolerability (National Cancer Institute Common Terminology Criteria for Adverse Events v5.0), maximum tolerated dose, and recommended dose for expansion. Key secondary objectives were the overall response rate (ORR, ≥minor response; International Workshop on WM 11 consensus criteria) and major response rate (MRR; ≥partial response).

Results: As of March 25, 2026, 43 pts with R/R WM had received tacabrutideg (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); these 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%]). Thirty-six pts (83.7%) discontinued prior BTKi due to progressive disease (PD). At baseline, the frequencies of gene mutations in WM cells (42 evaluable pts) were 19 (45.2%) for *CXCR4*, 23 (54.8%) for *TP53*, 13 (31.0%) for *BTK*, and 3 (7.1%) for *PLCG2*. Median study follow-up was 17.5 (range, 0.8-40.6) months. At data cutoff, 22 pts (51.2%) remained on treatment.

Median tacabrutideg exposure was 15.5 (range, 0.3-38.0) months. Overall, 97.7% of pts experienced any-grade treatment-emergent adverse events (TEAEs; grade ≥3, 69.8%). Any-grade TEAEs in ≥25% were neutropenia/neutrophil count decreased (37.2%), diarrhea (30.2%), and contusion (bruising; 27.9%). Examining the frequencies of new or ongoing any-grade TEAEs during the time period of 0 to <12 months compared with 12 to <24 months, the rates of neutropenia/neutrophil count decreased (37.2% vs 11.5%) and diarrhea (27.9% vs 19.2%) decreased in the second year, respectively. Grade ≥3 TEAEs in ≥10% included neutropenia/neutrophil count decreased (34.9%) and anemia

(14.0%). No atrial fibrillation occurred. As previously reported, 3 pts (7.0%) died due to TEAEs.

All 43 pts were response-evaluable. The ORR was 81.4% (n=35), the MRR was 74.4% (n=32), and the very good partial response rate was 30.2% (n=13). Median time to first overall response was 1.0 (range, 0.9-6.5) months and time to best overall response was 2.1 (range, 0.9-12.2) months. High ORRs and MRRs were observed in pts with disease bearing mutations in the following genes: *CXCR4* (94.7% [18/19] and 84.2% [16/19], respectively), *TP53* (both 87.0% [20/23]), *BTK* (both 100% [13/13]), and *PLCG2* (both 66.7% [2/3]). High ORR was observed in 77.8% (28/36) of pts who discontinued a prior BTK inhibitor due to PD. Pts with baseline anemia and treatment responses had rapid improvement in hemoglobin levels, from a median of 97.5 (range, 60.0-108.0) g/L at baseline (n=24) to 114.0 (range, 88.0-143.0) g/L at week 9 day 1 (n=23). Pts with baseline hypoalbuminemia (<35 g/L) and treatment responses had improvement in albumin levels from a median of 31.5 (range, 21-34.2) g/L at baseline (n=22) to 37 (range, 23-45) g/L at week 9 day 1 (n=19). The duration of response at 18 months was 71.7% among pts achieving ≥minor response (median follow-up in responders, 18.4 months). Median progression-free survival (PFS) follow-up was 19.3 (95% CI, 16.6-22.1) months; the estimated 18-month PFS rate was 68.4% (95% CI, 50.9%-80.7%).

Conclusions: Tacabrutideg had promising antitumor activity, including in pts with R/R WM bearing *CXCR4*, *TP53,* and *BTK* mutations. Pts with treatment responses experienced rapid improvement in cytopenia and hypoalbuminemia, and response was sustained over time. No new safety signals or TEAE-related deaths occurred in heavily pretreated pts with R/R WM in CaDAnCe-101. Phase 2 of this study is enrolling in pts with WM.