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Updated efficacy and safety of the Bruton tyrosine kinase (BTK) degrader tacabrutideg (BGB-16673) in BTK inhibitor–naive patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and other B-cell malignancies in the CaDAnCe-101 study

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Introduction: BTK is a key mediator of signaling pathways involved in the pathogenesis of many B-cell malignancies, and BTK inhibitors (BTKis) remain the standard of care for these malignancies. Tacabrutideg (BGB-16673) is a potential first-in-class oral BTK degrader that induces BTK degradation through the proteasome pathway, leading to tumor regression. CaDAnCe-101 (BGB-16673-101; NCT05006716) is an ongoing

phase 1/2 study evaluating tacabrutideg in patients (pts) with B-cell malignancies. Previous reports have shown promising tacabrutideg activity in heavily pretreated BTKi-exposed pts. Here we report the updated safety and efficacy of tacabrutideg in BTKi-naive pts with B-cell malignancies in phase 1 of CaDAnCe-101.

Methods: Eligible pts had a confirmed diagnosis of CLL/SLL, mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenström macroglobulinemia (WM), or Richter transformation (RT); had an ECOG performance status of 0-2 (0/1 in EU); and were BTKi naive. Tacabrutideg 200 mg was administered orally once daily. The primary objective was to assess safety; secondary objectives included assessing overall response rate (ORR), with the first assessment occurring after 12 weeks of treatment (4 weeks for WM).

Results: As of March 25, 2026, 65 pts (CLL/SLL, n=40; MCL, n=8; MZL, n=10; RT, n=2; WM, n=5) were enrolled and had received tacabrutideg. Median age was 67 (range, 42-81) years, and median number of prior therapies was 2 (range, 0-9). Overall, 23 pts (CLL, 21/40 [52.5%]; WM, 2/5 [40.0%]) were treatment naive (TN). In previously treated pts, prior therapies included an anti-CD20 antibody (n=42/42 [100%]), BCL2 inhibitor (n=5 [11.9%]), and chemotherapy (n=41 [97.6%]). Among pts with CLL/SLL, 19/25 (76.0%) had unmutated IGHV and 11/28 (39.3%) had del(17p) and/or *TP53* mutation. Median study follow-up was 10.8 (range, 0.8-16.1) months, and 52 pts (80.0%) remained on treatment at data cutoff.

Median tacabrutideg exposure was 10.4 (range, 0.7-16.1) months. Overall, 84.6% of pts had any-grade treatment-emergent adverse events (TEAEs), and 36.9% had grade ≥3 TEAEs. Any-grade TEAEs in ≥15% were contusion (bruising; 23.1%), petechiae (18.5%), neutropenia/neutrophil count decreased (18.5%), and anemia (15.4%). The most common grade ≥3 TEAE was neutropenia/neutrophil count decreased (13.8%). No major hemorrhage or invasive fungal infections occurred. One TEAE led to treatment discontinuation and death due to metastatic neoplasm, and 2 additional TEAEs led

to treatment discontinuation: 1 due to exacerbation of chronic back pain and 1 due to pleurisy. None of these TEAEs were considered treatment related, and all 3 pts had CLL/SLL. No TEAEs led to dose reduction. In pts with CLL/SLL, the most common grade ≥3 TEAE was neutropenia/neutrophil count decreased (17.5%).

Due to the small number of pts with non-CLL/SLL histologies, efficacy is reported only for CLL/SLL. In 30 evaluable pts with CLL/SLL, the ORR (partial response with lymphocytosis [PR-L] or better) was 80.0% (complete response, n=1; partial response, n=22; PR-L, n=1), with a median follow-up of 10.5 months. ORR was 84.6% (11/13; 2 had stable disease [SD]) in TN pts (median follow-up, 4.8 months) and 76.5% (13/17; 4 had SD) in pts with relapsed/refractory CLL/SLL (median follow-up, 12.9 months). No disease progression occurred, and all 24 responses were ongoing at data cutoff. Median time to first response was 2.8 (range, 2.7-5.6) months, corresponding to the time of first disease assessment. Responses occurred in all 17 pts with unmutated IGHV and in 6 of 9 (66.7%) with del(17p) and/or *TP53* mutation. Median progression-free survival was not reached. Available BTK degradation data for peripheral blood from 44 pts showed that all achieved complete degradation at steady state.

Conclusions: Updated phase 1 results continue to demonstrate that the novel BTK degrader tacabrutideg is well tolerated in BTKi-naive pts with B-cell malignancies. No major hemorrhage or invasive fungal infections occurred, and fewer grade ≥3 TEAEs were reported compared with heavily pretreated, BTKi-exposed cohorts. Tacabrutideg shows promising antitumor activity in BTKi-naive pts with CLL/SLL, with a high response rate and ongoing responses at data cutoff. This encouraging safety and efficacy will inform future clinical trials.