

Bruton tyrosine kinase (BTK) degrader BGB-16673 in BTK inhibitor-naïve patients with CLL/SLL and other B-cell malignancies: Results from the phase 1 CaDAnCe-101 study

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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. CaDAnCe-101 (BGB-16673-101; NCT05006716) is an ongoing open-label, phase 1/2 study of BGB-16673 monotherapy in patients (pts) with B-cell malignancies. Previous reports have shown promising activity of BGB-16673 in heavily pretreated pts exposed to BTK inhibitors. This is the first report on the safety/efficacy of a BTK degrader in BTK inhibitor-naïve pts.

Aims: To report safety and efficacy results for phase 1 of the CaDAnCe-101 trial in BTK inhibitor-naïve pts with B-cell malignancies.

Methods: Eligible pts had a confirmed diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenström macroglobulinemia (WM), or Richter transformation (RT); an ECOG performance status of 0-2 (0/1 in the EU); and no prior treatment with a BTK inhibitor. BGB-16673 was administered orally at 200 mg once daily. The primary objective was to evaluate 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 Dec 15, 2025, 54 pts (CLL/SLL, n=29; MCL, n=8; MZL, n=10; RT, n=2; WM, n=5) were enrolled and treated with BGB-16673. Median age was 68 (range, 42-81) years and pts had a median of 2 (range, 0-9) prior lines of therapy. Median follow-up was 8.3 (range, 0.4-12.8) months and 43 pts (79.6%) remained on treatment at data cutoff.

Any-grade treatment-emergent adverse events (TEAEs) occurred in 83.3% of pts; grade ≥ 3 TEAEs occurred in 33.3%. Any-grade TEAEs in $\geq 15\%$ of pts were contusion (bruising; 27.8%) and petechiae (18.5%). Grade ≥ 3 TEAEs in ≥ 2 pts were neutropenia/neutrophil count decreased (14.8%) and anemia, hypertension, lower respiratory tract infection, pneumonia, and thrombocytopenia (each 3.7%). No cases of major hemorrhage, opportunistic infections or febrile neutropenia occurred. TEAEs led to treatment discontinuation in 2 pts (3.7%; metastatic neoplasm, n=1; back pain, n=1; neither considered treatment related) and death in 1 pt (1.9%; metastatic neoplasm in the brain; not considered treatment related); all had CLL/SLL.

In pts with CLL/SLL (n=29), the most common grade ≥ 3 TEAE was neutropenia/neutrophil count decreased (20.7%).

In 22 evaluable pts with CLL/SLL, the ORR was 86.4% (partial response [PR], n=15; PR with lymphocytosis, n=4) with median follow-up of 8.2 months. At data cutoff, all responses were ongoing (n=19). Median time to first response was 2.8 (range, 2.7-5.6) months, around the time of first disease assessment. Responses occurred in all 4 pts with known unmutated IGHV and in 4 of 6 pts with known del(17p) and/or *TP53* mutation. At 6 months, no progression-free survival events were observed. Efficacy is not reported at this time in other cohorts due to small sample sizes.

BTK degradation data were available for 44 pts in peripheral blood; all showed complete BTK degradation at steady-state.

Summary/Conclusion: In a first report of BTK degrader clinical activity in a BTK inhibitor-naive population, BGB-16673 was well tolerated. Relative to BTK inhibitor-exposed pts, BTK inhibitor-naive pts had fewer grade ≥ 3 TEAEs and no reported opportunistic infections or major hemorrhage. BGB-16673 shows promising antitumor activity in BTK inhibitor-naive pts with CLL/SLL. This encouraging safety and efficacy could inform future clinical trials.