

Updated efficacy and safety of the Bruton tyrosine kinase degrader BGB-16673 in patients with relapsed or refractory CLL/SLL: Results from the ongoing phase 1 CaDAnCe-101 study

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ABSTRACT

Objective: Bruton tyrosine kinase (BTK) inhibitors are effective treatments for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), but intolerance and/or acquired resistance due to BTK mutations can emerge. 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. Here, updated phase 1 results are reported for patients with relapsed/refractory (R/R) CLL/SLL in CaDAnCe-101 (BGB-16673-101; NCT05006716), a phase 1/2 open-label study.

Methods: Eligible patients must have confirmed R/R CLL/SLL (≥ 2 prior therapies), an ECOG performance status of 0-2, and adequate organ function. In the US/EU/Australia, patients must have previously received a covalent BTK inhibitor (cBTKi). BGB-16673 was dosed once daily orally. Primary objectives were to assess safety/tolerability (Common Terminology Criteria for Adverse Events v5.0; International Workshop on CLL [iwCLL] hematologic toxicity criteria) and establish the maximum tolerated dose and recommended dose for expansion. A secondary objective was to assess overall response rate (ORR) per iwCLL 2018 criteria with partial response with lymphocytosis (PR-L) modification for CLL, and 2014 Lugano criteria for SLL.

Results: As of December 17, 2024, 66 patients with CLL/SLL were enrolled and treated (50 mg, n=1; 100 mg, n=22; 200 mg, n=16; 350 mg, n=15; 500 mg, n=12). Median age was 70 years (range, 47-91 years); the median number of prior therapies was 4 (range, 2-10), including prior cBTKis (n=61; 92.4%), BCL2 inhibitors (BCL2is; n=54; 81.8%), and noncovalent BTK inhibitors (ncBTKis; n=14; 21.2%). In total, 65.2% (43/66) of patients had del(17p) and/or TP53 mutation and 79.6% (39/49) had unmutated IGHV. Median follow-up was 13.1 months (range, 0.3-29.9 months).

Overall, 92.4% of patients had any-grade treatment-emergent adverse events (TEAEs; grade ≥ 3 , 51.5%). TEAEs in $\geq 30\%$ of patients were fatigue (36.4%; grade ≥ 3 , 1.5%) and contusion/bruising (30.3%; no grade ≥ 3). Grade ≥ 3 TEAEs in $\geq 10\%$ of patients were neutropenia/neutrophil count decreased (21.2%) and pneumonia (12.1%). Atrial fibrillation (grade 1 in the context of bacterial pneumonia) and febrile neutropenia (in the context of COVID-19 pneumonia and norovirus diarrhea) occurred in one patient (1.5%) each. Hypertension (n=2, both grade 3) and major hemorrhage occurred in two patients each (3.0%, grade 1 subarachnoid hemorrhage resolved; grade 3 subdural hemorrhage outcome unknown). Six patients (9.1%) had a TEAE leading to dose reduction. Four patients had TEAEs that led to death (pneumonia in the context of disease progression, septic

shock, bronchopulmonary & cerebral aspergillosis, and acute respiratory failure; n=1 each); no deaths were deemed related to BGB-16673.

In 66 response-evaluable patients, ORR (PR-L or better) was 80.3% (n=53), and complete response (CR)/complete response with incomplete marrow recovery (CRi) rate was 3.0% (n=2). At 200 mg, ORR was 93.8% (15/16), including one CR. Median time to first response was 2.8 months (range, 2.0-10.9 months). Thirty-three patients (50.0%) remained on treatment for ≥ 12 months; 38 patients had ongoing responses. Responses deepened over time: of 19 patients with initial PR-L, 10 transitioned to partial response (PR) and one to CR; of 15 patients with initial stable disease (SD), one transitioned to PR-L, five to PR, and one to CRi. Responses were seen at the lowest dose (50 mg, 1/1); in patients previously treated with a cBTKi (49/61; 80.3%) or ncBTKi (10/14; 71.4%) and with double- (cBTKi and BCL2i; 36/41; 87.8%) and triple-exposure (cBTKi, BCL2i, ncBTKi; 9/12; 75.0%); and in patients with (17/24; 70.8%) and without (33/39; 84.6%) *BTK* mutations and with del(17p) and/or *TP53* mutation (33/43; 76.7%). Median progression-free survival was not reached.

Conclusion: Data from this ongoing study demonstrate that the novel BTK degrader BGB-16673 has a tolerable safety profile and shows robust and deepening responses in patients with heavily pretreated R/R CLL/SLL, including those with prior BTK inhibitor treatment and BTK inhibitor mutations.