Updated efficacy and safety results of the Bruton tyrosine kinase (BTK) degrader BGB-16673 in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) from the ongoing phase 1 CaDAnCe-101 study

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Introduction: BTK inhibitors are effective treatments for CLL/SLL; however, treatment intolerance and resistance to BTK inhibitors are major clinical challenges for many patients. 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 phase 1 safety and efficacy data are reported for patients with relapsed/refractory (R/R) CLL/SLL.

Methods: Eligible patients must have confirmed R/R CLL/SLL (≥2 prior therapies), an ECOG performance status of 0-2 (0-1 in the EU), and adequate organ function. In the US, EU, and Australia, patients must have previously received a covalent BTK inhibitor (cBTKi). Patients received BGB-16673 once daily orally. The primary phase 1 objectives were to assess safety/tolerability (NCI-CTCAE v5.0; iwCLL hematologic toxicity criteria) and to 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 and per 2014 Lugano criteria for SLL, with the first response assessment after 12 weeks of treatment.

Results: As of May 23, 2025, 67 patients with CLL/SLL were enrolled and treated (50 mg, n=1; 100 mg, n=22; 200 mg, n=17; 350 mg, n=15; 500 mg, n=12). Patients had a median age of 70 years (range, 47-91 years) and a median of 4 prior lines of therapy

(range, 2-10), including cBTKis (n=63 [94.0%]), BCL2is (n=55 [82.1%]), and noncovalent BTK inhibitors (ncBTKis; n=14 [20.9%]). At study baseline, 65.7% (44/67) of patients had CLL/SLL with del(17p) and/or *TP53* mutation, 77.6% (38/49) with unmutated IGHV, 38.1% (24/63) with *BTK* mutation, and 15.9% (10/63) with *PLCG2* mutation. Median study follow-up was 18.0 months (range, 0.3-31.0 months); 39 patients (58.2%) remained on treatment at the data cutoff.

Overall, 95.5% of patients had any-grade treatment-emergent adverse events (TEAEs); any-grade TEAEs in ≥25% of patients were fatigue (37.3%), contusion/bruising (31.3%), diarrhea (28.4%), and neutropenia (28.4%). Grade ≥3 TEAEs occurred in 62.7% of patients; grade ≥3 TEAEs in ≥5% of patients were neutropenia (23.9%), pneumonia (10.4%), and thrombocytopenia (6.0%). Eight patients (11.9%) had a TEAE leading to dose reduction. TEAEs led to treatment discontinuation in 12 patients (17.9%), three (4.5%) of whom had treatment-related TEAEs (subdural hemorrhage, maculopapular rash, and disseminated aspergillosis). Four patients (6.0%) had TEAEs that led to death (all due to infections, including 1 fungal infection); no deaths were deemed related to treatment.

In 66 response-evaluable patients (1 patient on treatment did not reach the first assessment by the data cutoff), ORR (PR-L or better) was 86.4% (n=57), with a 4.5% (n=3) complete response (CR)/CR with incomplete marrow recovery rate. At 200 mg, ORR was 93.8% (15/16), including 1 CR. The median time to first response was 2.8 months (range, 2.0-19.4 months). Thirty-three patients (49.3%) remained on treatment for ≥12 months. Responses deepened over time: of 22 patients with initial PR-L, 15 transitioned to partial response (PR); of 16 patients with initial stable disease, 1 transitioned to PR-L and 10 to PR. Responses were seen in patients previously treated with a cBTKi (53/62 [85.5%]) or ncBTKi (10/14 [71.4%]), with double (cBTKi and BCL2i; 39/42 [92.9%]) and triple exposure (cBTKi, BCL2i, and ncBTKi; 9/12 [75.0%]), with (18/24 [75.0%]) and without (36/39 [92.3%]) *BTK* mutations, with del(17p) and/or *TP53* mutation (35/43 [81.4%]), and with *PLCG2* mutation (9/10 [90.0%]). The 12-month progression-free survival rate was 79.2%; 15 patients (22.4%) had progressive disease (2 associated with Richter transformation to diffuse large B-cell lymphoma), and 4 (6.0%) died. Further exploratory analyses will be presented at the meeting.

Conclusions: Data from the ongoing CaDAnCe-101 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* mutations. The 200-mg dose of BGB-16673 is being evaluated in phase 2 and 3 studies in patients with R/R CLL/SLL.