Preliminary efficacy and safety of the Bruton tyrosine kinase degrader BGB-16673 in patients with relapsed/refractory Richter transformation: Results from the ongoing phase 1 CaDAnCe-101 study

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Introduction: There is no standard of care treatment for Richter transformation (RT) of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) to diffuse large B-cell lymphoma (DLBCL). Existing therapies, including chemoimmunotherapy (CIT) and Bruton tyrosine kinase (BTK) inhibitors ± checkpoint inhibitors, may induce responses, but they are not durable and patient outcomes are poor. 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, preliminary safety and efficacy results of BGB-16673 are presented in patients with relapsed/refractory (R/R) RT who were treated in the phase 1 portion of the study.

Methods: Eligible patients must have confirmed R/R RT treated with ≥1 prior RT-directed therapy, an ECOG performance status of 0-2 (0-1 in the EU), and adequate organ function; patients with progressive CLL/SLL who had a prior history of RT were included in the RT cohort. In the US, EU, and Australia, patients must have previously received a covalent BTK inhibitor. BGB-16673 was dosed once daily (QD) orally in 28-day cycles (6 planned dose levels: 50-600 mg QD). The primary phase 1 objectives were to assess safety and tolerability per NCI-CTCAE v5.0 and to establish the maximum tolerated dose and recommended dose for expansion. A secondary objective was to assess the overall response rate (ORR) per 2014 Lugano criteria, with the first assessment occurring after 12 weeks of treatment.

Results: As of May 23, 2025, 24 patients with RT were enrolled and treated in 1 of 4 BGB-16673 dose cohorts (100 mg, n=5; 200 mg, n=7; 350 mg, n=10; 500 mg, n=2). Median age in all patients was 67 years (range, 47-83 years). The median number of

prior therapies for either CLL/SLL or RT was 3 (range, 1-11), of which a median of 2 (range, 1-11) were given for RT. Prior therapies included covalent BTK inhibitors (n=20 [83.3%]), BCL2 inhibitors (n=13 [54.2%]), noncovalent BTK inhibitors (n=4 [16.7%]), allogeneic or autologous stem cell transplant (SCT; n=2 [8.3%] each), and chimeric antigen receptor-T cell therapy (n=1 [4.2%]). All patients received CIT for RT prior to study enrollment (23/24 received anthracycline-based CIT). Overall, 19.0% of patients (4/21) had *BTK* mutations prior to BGB-16673 treatment. At baseline, 83.3% (20/24) of patients had *TP53* mutation, 90.9% (10/11) had unmutated IGHV, and 23.8% (5/21) had *PLCG2* mutation. Median follow-up was 5.2 months (range, 0.6-17.8 months).
In total, 91.7% of patients had any-grade treatment-emergent adverse events (TEAEs) and 66.7% had grade ≥3 TEAEs. Any-grade TEAEs that occurred in ≥15% of patients were neutropenia/neutrophil count decreased (37.5%), nausea (20.8%), diarrhea (16.7%), peripheral edema (16.7%), and pneumonia (16.7%). Grade ≥3 TEAEs that occurred in ≥10% of patients were neutropenia/neutrophil count decreased (33.3%), anemia (12.5%), and pneumonia (12.5%). No cases of atrial fibrillation or febrile neutropenia occurred. Major hemorrhage occurred in 4.2% of patients (n=1; grade 2 subdural hematoma). TEAEs led to dose reductions in 2 patients (8.3%) and to death in 1 patient (4.2%; pyrexia in the context of progressive disease, not deemed to be treatment related).
In 21 response-evaluable patients (3 patients with ongoing treatment had not reached the first response assessment by the data cutoff), the ORR was 52.4% (n=11), including a complete response rate of 9.5% (n=2). One patient with an ongoing response discontinued treatment to undergo allogeneic SCT. Responses were seen in 55.6% of patients (10/18) previously treated with a covalent BTK inhibitor, in patients with (4/4 [100%]) and without (7/17 [41.2%]) known *BTK* mutations, with *TP53* mutations (9/18 [50.0%]), and with *PLCG2* mutations (2/5 [40.0%]). Median time to first response was 2.8 months (range, 2.6-4.6 months). Among the 11 patients who attained a response, 5 maintained a response for ≥6 months; of the remaining patients, 3 were censored and 3 experienced events prior to 6 months.

Conclusions: Data from this ongoing study demonstrate that the BTK degrader BGB-16673 has a tolerable safety profile and a promising ORR of 52.4%, with evidence of responses lasting >6 months in heavily pretreated patients with R/R RT.