Preliminary efficacy and safety of the Bruton tyrosine kinase degrader BGB-16673 in patients with relapsed or refractory Waldenström macroglobulinemia: Results from the phase 1 CaDAnCe-101 study

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Introduction: Bruton tyrosine kinase (BTK) inhibitors are highly effective against Waldenström macroglobulinemia (WM). Their effectiveness can be limited by resistance caused by BTK mutations and intolerance. BGB-16673 is a bivalent small molecule that induces BTK degradation by binding specifically to BTK and the E3 ligase. The E3 ligase catalyzes the transfer of ubiquitin molecules to BTK, which marks BTK for destruction by the proteasome. Preclinically, BGB-16673 degraded wild-type and mutant BTK associated with covalent and noncovalent BTK inhibitors (ncBTKis), leading to tumor suppression. CaDAnCe-101 (BGB-16673-101; NCT05006716) is an ongoing, open-label, first-in-human, phase 1/2 study evaluating BGB-16673 monotherapy in patients with a range of B-cell malignancies. Here, early results in patients with WM enrolled in the phase 1 portion are presented.

Methods: Eligible patients must have confirmed R/R WM (≥2 prior therapies), an ECOG performance status of 0-2, and adequate organ function. Patients must have previously received an anti-CD20 antibody and, in the US and EU, a covalent BTK inhibitor (cBTKi). BGB-16673 was orally dosed once daily in 28-day cycles. Dose escalation used a Bayesian optimal

interval design (6 planned dose levels, 50-600 mg once daily). Primary objectives were to evaluate safety/tolerability (CTCAE v5.0) and to establish the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). Dose-limiting toxicities (DLTs) were assessed in the first 4 weeks (cycle 1). A secondary objective was to evaluate the overall response rate (ORR, IWWM-6 consensus criteria), with the first assessment occurring after 4 weeks of treatment.
Results: As of May 24, 2024, 22 patients with WM were enrolled and treated (100 mg, n=4; 200 mg, n=10; 350 mg, n=8). The median age was 73.0 (range, 56-81) years, and the median number of prior therapies was 3.5 (range, 2-11), including prior cBTKis (n=22 [100%]), BCL2 inhibitors (n=4 [18%]), and ncBTKis (n=3 [14%]). Twenty patients (91%) had previously received chemotherapy. According to the International Prognostic Scoring System for WM, 6 patients (27%) had low-risk disease, 7 (32%) had intermediate-risk disease, and 8 (36%) had high-risk disease (missing/unknown data, n=1). Five patients (23%) had BTK mutations, 20 (91%) had *MYD88* mutations, and 8 (36%) had *CXCR4* mutations. The median follow-up was 4.3 (range, 0.3-21.3) months.

Ninety-five percent of patients reported any-grade treatment-emergent adverse events (TEAEs; grade ≥3, 45%; serious, 23%), the most common (≥20%) of which were neutropenia/neutrophil count decreased (32%; grade ≥3, 23%), contusion (23%; no grade ≥3), and diarrhea (23%; no grade ≥3). The most common grade ≥3 TEAE (≥20%) was neutropenia/neutrophil count decreased. No atrial fibrillation, hypertension, febrile neutropenia, or major hemorrhage occurred. Three patients (14%) had a grade ≥3 infection (bronchopulmonary/cerebral aspergillosis, septic shock, and pseudomonal bacteremia/sinusitis). No patients had a TEAE that led to treatment discontinuation or dose reduction. No DLTs occurred, and the MTD was not reached. One patient (5%) died due to a TEAE (septic shock, considered related to disease progression). One patient died due to disease progression.

In 21 response-evaluable patients (1 too early), the ORR (minor response or better) was 90%, the major response rate (partial response [PR] or better) was 81%, and the very good PR or better rate was 14%. Median time to first response was 0.95 (range, 0.9-3.7) months, with responses deepening over time. Seventeen patients remain on treatment and have ongoing responses. Responses were seen at the lowest dose (100 mg, 4/4), in patients previously treated with a cBTKi (19/21) and an ncBTKi (3/3), and in patients discontinued from prior BTKi due to disease progression (15/17). In addition, responses were observed in patients with and without mutations in *BTK* (with, 5/5; without, 6/8; unknown, 8/8), *MYD88* (with, 18/20; without, 1/1), and *CXCR4* (with, 8/8; without, 11/13). One patient had IgM flare at initial response assessment and went on to develop PR.

Conclusions: Early data from this ongoing, first-in-human study demonstrate that the novel BTK degrader BGB-16673 has a tolerable safety profile and shows promising antitumor activity in heavily pretreated patients with BTK inhibitor–exposed R/R WM, including those with *BTK* and *CXCR4* mutations.