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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ABSTRACT

Introduction: Bruton tyrosine kinase (BTK) inhibitors are highly effective against Waldenström macroglobulinemia (WM), but their effectiveness can be limited by resistance and intolerance. BGB-16673 is a bivalent small molecule that induces BTK degradation via polyubiquitination. 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 phase 1 results are presented in patients with WM.

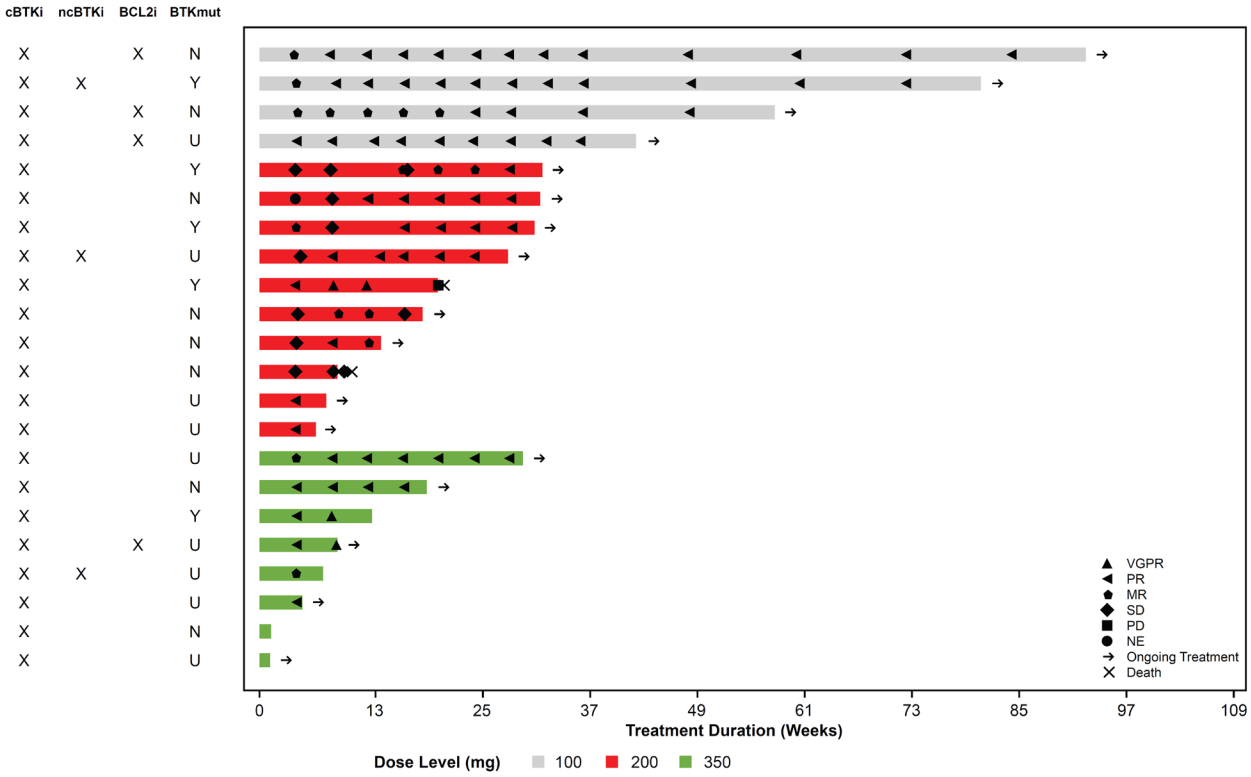
Methods: Eligible patients must have confirmed R/R WM (≥2 prior therapies), ECOG performance status 0-2, and adequate organ function. Patients must have previously received an anti-CD20 antibody and, in the US and EU, a covalent BTK inhibitor (cBTKi). BGB-16673 was orally dosed once daily in 28-day cycles. 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 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 median number of prior therapies was 3.5 (range, 2-11), including prior cBTKis (n=22 [100%]), BCL2 inhibitors (n=4 [18%]), and noncovalent BTK inhibitors (ncBTKis; n=3 [14%]). 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%) 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 was neutropenia/neutrophil count decreased. No atrial fibrillation, hypertension, febrile

neutropenia, or major hemorrhage occurred. No patient 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) related to disease progression. In 21 response-evaluable patients, the ORR (minor response or better) was 90%, the major response rate (partial response or better) was 81%, and the very good partial response or better rate was 14% (Figure). Median time to first response was 0.95 (range, 0.9-3.7) months, with responses deepening over time. 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 BTKi due to disease progression (15/17). 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).

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.

Figure. Treatment Duration and Response Assessment



BTK mutation status classified as present (Y), absent (N), or unknown (U).
BCL2i, BCL2 inhibitor; cBTKi, covalent BTK inhibitor; MR, minor response; ncBTKi, noncovalent BTK inhibitor; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.