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: BGB-16673 is a bivalent small molecule that induces BTK degradation by binding BTK and E3 ligase. CaDAnCe-101 (BGB-16673-101; NCT05006716) is an ongoing, open-label, phase 1/2 study of BGB-16673 monotherapy in patients (pts) with B-cell malignancies. Here, early phase 1 results for WM are presented.

Methods: Eligible pts had ≥2 prior WM therapies, including anti-CD20 antibody and covalent BTK inhibitor (cBTKi; US/EU only). BGB-16673 was orally dosed once daily in 28-d cycles (6 planned doses: 50-600mg). Primary objectives were to assess safety/tolerability (CTCAEv5.0) and establish maximum tolerated dose (MTD) and recommended dose for expansion. Dose-limiting toxicities (DLTs) were assessed in cycle 1 (4 wks). A secondary objective was to evaluate overall response rate (ORR, IWWM-6 criteria) beginning after 4 wks of treatment.

Results: As of 24 May 2024, 22 pts with WM were enrolled and treated (100mg, n=4; 200mg, n=10; 350mg, n=8). Median age was 73.0 y (range, 56-81). The median number of prior therapies was 3.5 (range, 2-11; cBTKi, n=22; BCL2i, n=4; ncBTKi, n=3; chemotherapy, n=20). Per the IPSSWM, 27%, 32%, and 36% had low-, intermediate-, or high-risk disease, respectively. Mutations were seen in *BTK* (23%), *MYD88* (91%), and *CXCR4* (36%). Median follow-up was 4.3 mo (range, 0.3-21.3). Any-grade (gr) treatment-emergent adverse events (TEAEs) were reported in 95% (gr ≥3, 45%; serious, 23%). TEAEs in ≥20% of pts were neutropenia/neutrophil count decreased (32%; gr ≥3, 23%), contusion (23%; no gr ≥3), and diarrhea (23%; no gr ≥3). No atrial fibrillation, hypertension, febrile neutropenia, or major hemorrhage occurred. 3 pts (14%) had a gr ≥3 infection (bronchopulmonary/cerebral aspergillosis, septic shock, pseudomonal bacteremia/sinusitis). No TEAEs led to treatment discontinuation or dose reduction. No DLTs occurred; MTD was not reached. 1 pt (5%) died due to a TEAE (septic shock related to PD); 1 died of PD. In 21 evaluable pts (1 too early), ORR (≥minor response) was 90%, major response rate (≥partial response [PR]) was 81%, very good PR or better rate was 14%. Median time to first response was 0.95 mo (range, 0.9-3.7); responses deepened over time. 17 pts remain on treatment with

ongoing responses. Responses were seen at the lowest dose (100 mg, 4/4), in those with prior cBTKi (19/21) and ncBTKi (3/3), and in pts discontinued from prior BTKi due to PD (15/17). In addition, responses were seen in pts with (w) and without (wo) mutations in *BTK* (w, 5/5; wo, 6/8; unknown: 8/8), *MYD88* (w, 18/20; wo, 1/1), and *CXCR4* (w, 8/8; wo, 11/13). 1 pt had IgM flare at initial response assessment and went on to develop PR.

Conclusions: Early data from this ongoing study show that novel BTK degrader BGB-16673 is tolerable and has promising antitumor activity in heavily pretreated pts with BTKi–exposed R/R WM, including that with *BTK* and *CXCR4* mutations.