UPDATED EFFICACY & SAFETY OF THE BRUTON TYROSINE KINASE (BTK) DEGRADER BGB-16673 IN PATIENTS WITH RELAPSED/REFRACTORY WALDENSTRÖM MACROGLOBULINEMIA (WM): ONGOING PHASE (PH) 1 CADANCE-101 STUDY RESULTS

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Background: BTK inhibitors are highly effective against WM, but resistance and intolerance can emerge. BGB-16673 is a potential first-in-class protein degrader that blocks BTK signalling by tagging BTK for degradation through the cell's proteasome pathway. CaDAnCe-101 (BGB-16673-101; NCT05006716) is an ongoing, open-label, phase 1/2 study evaluating BGB-16673 monotherapy in patients (pts) with a range of B-cell malignancies.

Aims: To present safety and efficacy of BGB-16673 in pts with WM in the phase 1 portion of the study.

Methods: Eligible pts must have confirmed R/R WM (≥2 prior therapies), an ECOG performance status of 0-2, previous receipt of an anti-CD20 antibody, and, in the US/EU, a covalent BTK inhibitor (cBTKi). BGB-16673 was dosed once daily orally. Primary objectives were to evaluate safety and tolerability (CTCAE v5.0) and establish the maximum tolerated dose and recommended dose for expansion. A secondary objective was to evaluate the overall response rate (ORR; modified IWWM-6 consensus criteria), with first assessment after 4 wk of treatment (tx).

Results: As of December 17, 2024, 30 pts with WM were enrolled and treated (100mg, n=10; 200mg, n=11; 350mg, n=9). Median age was 72.5 y (range, 56-81), and median number of prior therapies was 3 (range, 2-11), including prior cBTKis (n=30; 100%), BCL2 inhibitors (n=7; 23.3%), and noncovalent BTK inhibitors (ncBTKis; n=4; 13.3%). In total, 37.9% of pts (11/29) and 51.7% of pts (15/29) had *BTK* and *TP53* mutations, respectively. Median follow-up was 8.1 mo (range, 0.3-28.1). Overall, 96.7% of pts reported any-grade tx-emergent AEs (TEAEs; grade ≥3, 56.7%; serious, 30%), the most common (≥20%) being neutropenia/neutrophil count decreased (43.3%; grade ≥3, 33.3%), diarrhea (30.0%; no grade ≥3), contusion/bruising (26.7%; no grade ≥3), anemia (23.3%; grade ≥3, 16.7%), pyrexia (20.0%; grade ≥3, 3.3%), and thrombocytopenia (20.0%; grade ≥3, 6.7%). The most common grade ≥3 TEAE was neutropenia/neutrophil count decreased. No atrial fibrillation, febrile neutropenia, or major hemorrhage occurred. One case of grade 2 hypertension was observed. Five pts (16.7%) had a grade ≥3 infection (including 1 case of bronchopulmonary/cerebral aspergillosis). One pt had a TEAE (anemia) that led to tx discontinuation; 2 pts had a TEAE that led to dose reduction. One pt died due to a TEAE (septic shock in the context of progressive disease [PD]) and another due to PD.
In 29 response-evaluable pts, the ORR (minor response or better) was 89.7%, major response rate was 75.9% (n=22), and very good partial response rate was 31.0% (n=9). Median time to first response was 0.95 mo (range, 0.9-3.9), and median time to major response was 1.9 mo (range, 0.9-

6.4), with responses deepening over time. Twenty-two pts (73.3%) remain on tx and have ongoing responses. Responses were seen at the lowest dose (100mg, 10/10), in pts previously treated with a cBTKi (26/29 [89.7%]) and an ncBTKi (4/4 [100%]), and in pts who discontinued prior BTK inhibitor due to PD (21/23 [91.3%]). Responses were independent of mutations in *BTK* (with, 11/11; without, 14/17), *MYD88* (with, 23/25; without, 2/3), *CXCR4* (with, 14/14; without, 11/14), and *TP53* (with, 15/15; without, 10/13). Median PFS was not reached (**Figure**).

Summary/Conclusion: Data from this ongoing study demonstrate that the novel BTK degrader BGB-16673 was well tolerated and continued to show substantial antitumor activity in pts with heavily pretreated BTK inhibitor–exposed R/R WM, including those with *BTK, CXCR4,* and *TP53* mutations.

Figure. PFS in Patients with R/R WM