Updated efficacy & safety of the Bruton tyrosine kinase degrader BGB-16673 in patients with relapsed/refractory Waldenström macroglobulinemia: ongoing phase 1 CaDAnCe-101 study results

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ABSTRACT

Objective: Bruton tyrosine kinase (BTK) inhibitors are highly effective against Waldenström macroglobulinemia (WM), but resistance and intolerance can emerge. 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 a range of B-cell malignancies. Presented here are updated safety and efficacy results of BGB-16673 in patients with WM in the phase 1 portion of the study.

Methods: Eligible patients must have confirmed relapsed/refractory (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 (Common Terminology Criteria for Adverse Events 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 four weeks of treatment.

Results: As of December 17, 2024, 30 patients with WM were enrolled and treated (100 mg, n=10; 200 mg, n=11; 350 mg, n=9). Median age was 72.5 years (range, 56-81 years), 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 patients (11/29) and 51.7% of patients (15/29) had *BTK* and *TP53* mutations, respectively. Median follow-up was 8.1 months (range, 0.3-28.1 months).

Overall, 96.7% of patients reported any-grade treatment-emergent adverse events (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 two hypertension was observed. Five patients (16.7%) had a grade ≥3 infection (including one case of bronchopulmonary/cerebral aspergillosis). One patient had a TEAE (anemia) that led to treatment discontinuation; two patients had a TEAE that led to dose reduction. One patient died due to a TEAE (septic shock in the context of progressive disease [PD]) and another due to PD.

In 29 response-evaluable patients, 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 months (range, 0.9-3.9 months), and median time to major response was 1.9 months (range, 0.9-6.4 months), with responses deepening over time. Twenty-two patients (73.3%) remain on treatment and have ongoing responses. Responses were seen at the lowest dose (100 mg, 10/10), in patients previously treated with a cBTKi (26/29 [89.7%]) and an ncBTKi (4/4 [100%]), and in patients 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 progression-free survival was not reached.

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 patients with heavily pretreated BTK inhibitor–exposed R/R WM, including those with *BTK, CXCR4,* and *TP53* mutations.