Preliminary safety and efficacy of Bruton tyrosine kinase degrader BGB-16673 in patients with relapsed/refractory b-cell malignancies: Results from BGB-16673-102

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ABSTRACT

Objective: Covalent Bruton tyrosine kinase (cBTK) inhibitors have transformed the therapeutic landscape for patients with B-cell malignancies, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and Waldenström macroglobulinemia (WM). However, treatment resistance due to BTK mutations is an emerging challenge in clinical practice. Therefore, novel options that can overcome cBTK inhibitor resistance are needed.

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. In preclinical models, BGB-16673 showed central nervous system penetration and degraded both wild-type and mutant BTK resistant to cBTK and noncovalent BTK inhibitors. CaDAnCe-102 (BGB-16673-102; NCT05294731) is a multicenter, open label, phase 1/2 study designed to evaluate BGB-16673 monotherapy in patients with B-cell malignancies in China. Here, preliminary safety and efficacy data from phase 1 in Chinese patients with relapsed/refractory (R/R) B-cell malignancies are presented.

Methods: Eligible patients had R/R CLL/small lymphocytic lymphoma (SLL), WM, MCL, MZL, non-germinal center B-cell diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), or Richter transformation (RT). Patients must have received prior therapy (≥2 prior therapies for FL, WM, or MZL; ≥1 for all others), including a BTK inhibitor for patients with CLL/SLL, WM, or MCL. Additional eligibility criteria include an ECOG performance status of 0-2 and adequate organ function. BGB-16673 was orally administered once daily (QD). Dose escalation using a Bayesian optimal interval design with six dose levels (50-600 mg once daily) was planned. The primary objectives were to assess safety per NCI-CTCAE v5.0 in all patients and per iwCLL criteria for hematologic toxicity in patients with CLL; and to determine the recommended phase 2 dose (RP2D) and maximum tolerated dose (MTD). Dose-limiting toxicities (DLTs) were assessed over the first 28 days. A secondary objective was to assess the overall response rate (ORR) per Lugano criteria for SLL, DLBCL, FL, RT, MZL, and MCL; iwCLL 2018 criteria for CLL; and iwWM-11 criteria for WM.

Results: As of April 11, 2025, 55 patients (CLL/SLL, n=7; MCL, n=15; MZL, n=12; WM, n=5; DLBCL, n=11; FL, n=5) were enrolled and treated in phase 1 (50 mg, n=6; 100 mg, n=6; 200 mg, n=20; 350 mg, n=20; 500 mg, n=3); 24 patients remained on treatment. For all patients, the median age was 63 years (range, 25-82 years), and the median number of prior therapies was 3 (range, 1-7), including prior cBTK inhibitors (n=36, 65.5%), immunomodulatory drugs (n=17, 30.9%), and BCL2 inhibitors (n=7, 12.7%). The median follow-up time was 7.4 months (range, 0.6-34.2 months). Overall, 98.2% of patients reported treatment-emergent adverse events (TEAEs) of any grade and 65.5% had grade ≥3 TEAEs. The most common TEAEs were

thrombocytopenia/platelet count decreased (50.9%), neutropenia/neutrophil count decreased (41.8%), and hyperuricemia (36.4%, all events were grade 1 without concurrent signs/symptoms). The most common grade ≥3 TEAEs were neutropenia/neutrophil count decreased (25.5%), white blood cell count decreased (18.2%), and pneumonia (16.4%). No atrial fibrillation occurred. Two patients (3.6%) experienced a treatment-related TEAE leading to dose reduction (purpura, n=1; pyrexia, n=1), both treated at the 350-mg dose level. No patients reported treatment-related TEAEs that led to treatment discontinuation or death. In 47 response-evaluable patients, the ORR was 57.4%. Six patients had a complete response (MCL, n=3, including one patient who was heavily pretreated with 7 prior lines of therapy; DLBCL, FL, or MZL, n=1 each). One patient with WM who had 4 prior lines of therapy had a very good partial response. The median time to first response was 2.8 months (range, 1.8-11.1 months).

Conclusion: Preliminary data from this ongoing study demonstrate that BGB-16673 has a tolerable safety profile and elicits clinical responses in heavily pretreated patients with B-cell malignancies, including those with BTK inhibitor-resistant disease.