

Preliminary efficacy and safety of the Bruton tyrosine kinase degrader BGB-16673 in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: 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 the E3 ligase. CaDAnCe-101 (BGB-16673-101, NCT05006716) is an ongoing, open-label, phase 1/2 study of BGB-16673 monotherapy for B-cell malignancies. Updated phase 1 results in Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) are presented.

Methods: Patients had ≥ 2 prior CLL therapies, including a covalent BTK inhibitor (cBTKi; US/EU/Australia only). BGB-16673 was administered orally, once daily, in 28-d cycles (6 planned doses, 50-600 mg). Primary objectives were to assess safety/tolerability (CTCAEv5.0, iwCLL hematologic toxicity criteria) and establish maximum tolerated dose (MTD) and recommended dose for expansion. Dose-limiting toxicities (DLTs) were assessed in cycle 1 (4 weeks). A secondary objective was to evaluate ORR (iwCLL 2018 or Lugano 2014 SLL criteria), with first assessment after 12 weeks of treatment.

Results: As of 24May2024, 49 patients with CLL were enrolled and treated (50 mg, n=1; 100 mg, n=5; 200 mg, n=16; 350 mg, n=15; 500 mg, n=12). Median age was 70 y (range, 50-91); patients had a median of 4 prior therapies (range, 2-10; cBTKis, 92%; BCL2is, 86%; noncovalent BTKis [ncBTKis], 24%). Of tested patients, 63% (31/49) had del(17p) and/or TP53 mutation; 82% (32/39) had unmutated IGHV. Median follow-up was 7.9 months (range, 0.3-23.1). Treatment-emergent adverse events (TEAEs) occurred in 96% of patients (grade ≥ 3 , 57%); TEAEs in $\geq 25\%$ were fatigue (35%; grade ≥ 3 , 2%), contusion (29%; no grade ≥ 3), and diarrhea (27%; grade ≥ 3 , 2%). Grade ≥ 3 TEAEs in $\geq 10\%$ were neutropenia/neutrophil count decreased (20%) and pneumonia (10%). One patient each experienced hypertension, febrile neutropenia, and major hemorrhage; none experienced atrial fibrillation. Three patients (6%) had TEAEs leading to dose reduction. One DLT occurred (200 mg; grade 3 maculopapular rash). MTD was not reached. Three patients had TEAEs leading to death; none were treatment-related. In 49 evaluable patients, ORR (\geq partial response with lymphocytosis) was 78% and CR/CRi rate was 4%. At 200mg, ORR was 94% with 6% CR. Median time to first response was 2.8 months (range, 2.6-8.3). Seventeen patients remained on treatment for ≥ 9 months; all have ongoing responses. Responses were seen in patients

with prior cBTKi and ncBTKi, in double-exposed (cBTKi and BCL2i) and triple-exposed (cBTKi, BCL2i, ncBTKi) patients, and in those with and without *BTK* mutations.

Conclusions: Data from this ongoing study demonstrate that the novel BTK degrader BGB-16673 has a tolerable safety profile and show promising and deep responses in heavily-pretreated patients with R/R CLL/SLL, including those with prior BTKi treatment and BTK resistance mutations.