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

Authors: Meghan C. Thompson,[1] Ricardo D. Parrondo,[2] Anna Maria Frustaci,[3] John N. Allan,[4] Paolo Ghia,[5,6] Irina Mocanu,[7] Constantine S. Tam,[8] Judith Trotman,[9] Inhye E. Ahn,[10] Stephan Stilgenbauer,[11] Lydia Scarfo,[5,6] Xiangmei Chen,[12] Kunthel By,[13] Shannon Fabre,[13] Daniel Persky,[13] Amit Agarwal,[13] John F. Seymour[14]

Affiliations: [1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Mayo Clinic - Jacksonville, Jacksonville, FL, USA; [3]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [4]Weill Cornell Medicine, New York, NY, USA; [5]Università Vita-Salute San Raffaele, Milano, Italy; [6]IRCCS Ospedale San Raffaele, Milano, Italy; [7]Institute of Oncology, ARENSIA Exploratory Medicine, Düsseldorf, Germany; [8]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [9]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [10]Dana-Farber Cancer Institute, Boston, MA, USA; [11]Ulm University, Ulm, Germany; [12]BeiGene (Shanghai) Co, Ltd, Shanghai, China; [13]BeiGene USA, Inc, San Mateo, CA, USA; [14]Peter MacCallum Cancer Centre, Royal Melbourne Hospital, and University of Melbourne, Melbourne, VIC, Australia

Introduction: Bruton tyrosine kinase (BTK) inhibitors are effective therapies for the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Their use can be limited by intolerance and/or acquired resistance, due to *BTK* mutations. BGB-16673 is a bivalent small molecule that induces BTK degradation by binding specifically to BTK and the E3 ligase. The E3 ligase catalyzes the transfer of ubiquitin molecules to BTK which marks BTK for destruction by the proteasome. In preclinical models, BGB-16673 degraded wild-type and mutant forms of BTK associated with resistance to covalent and noncovalent BTK inhibitors, leading to tumor suppression. CaDAnCe-101 (BGB-16673-101, NCT05006716) is an ongoing, open-label, first-in-human, phase 1/2 study designed to evaluate BGB-16673 monotherapy in patients with B-cell malignancies. Here, updated results in patients with relapsed or refractory (R/R) CLL/SLL enrolled in the phase 1 portion are presented.

Methods: Eligible patients must have confirmed R/R CLL/SLL (≥2 prior therapies), an ECOG performance status of 0-2, and adequate organ function. In the US, EU, and Australia, patients must have previously received a covalent BTK inhibitor (cBTKi). BGB-16673 was dosed once daily orally in 28-day cycles. Dose escalation used a Bayesian optimal interval design (6 planned dose levels, 50-600 mg once daily). Primary objectives were to assess safety/tolerability (CTCAE v5.0 and iwCLL hematologic toxicity criteria), and to establish the maximum tolerated dose (MTD) and the recommended phase 2 dose. Dose-limiting toxicities (DLTs) were assessed in the first 4 weeks (cycle 1). A secondary objective was to evaluate the overall response rate (ORR, iwCLL 2018 criteria or 2014 Lugano criteria for SLL), with the first assessment occurring after 12 weeks of treatment.

Results: As of May 24, 2024, 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). The median age was 70 years (range, 50-91 years), and the median number of prior therapies was 4 (range, 2-10), including prior cBTKis (n=45 [92%]), BCL2 inhibitors (n=42 [86%]), and noncovalent BTK inhibitors (ncBTKis; n=12 [24%]). Of tested patients, 63% (31/49) had del(17p) and/or *TP53* mutation and 82% (32/39) had unmutated IGHV. The median follow-up was 7.9 months (range, 0.3-23.1 months).

Ninety-six percent of patients reported any-grade treatment-emergent adverse events (TEAEs; grade ≥3, 57%), of which the most common (≥25%) were fatigue (35%; grade ≥3, 2%), contusion (29%; no grade ≥3), and diarrhea (27%; grade ≥3, 2%). The most common grade ≥3 TEAEs (≥10%) were neutropenia/neutrophil count decreased (20%) and pneumonia (10%). One patient (2%) each experienced hypertension (grade 1), febrile neutropenia (in the context of COVID-19 pneumonia and norovirus diarrhea), and major hemorrhage. No atrial fibrillation was observed. Three patients (6%) experienced a TEAE that led to dose reduction. One DLT occurred in 1 patient at 200 mg (grade 3 maculopapular rash on day 27; decreased to grade 1 after 5-day hold; patient continues on treatment). The MTD was not reached. Three patients had TEAEs that led to death (septic shock, bronchopulmonary aspergillosis/cerebral aspergillosis, and pneumonia in the context of disease progression; n=1 each); none of the deaths were considered related to treatment.

In 49 response-evaluable patients, the ORR (partial response with lymphocytosis or better) was 78% (38/49), and the CR/CR with incomplete hematologic recovery rate was 4% (n=2). At 200 mg, the ORR was 94% (15/16) including the 2 CRs. Median time to first response was 2.8 months (range, 2.6-8.3 months). Seventeen patients remained on treatment for ≥9 months and all 17 have ongoing responses. Responses were seen at the lowest dose, as well as in patients previously treated with a cBTKi, ncBTKi, double- (cBTKi and BCL2i) and triple- (cBTKi, BCL2i, ncBTKi) exposed patients, and in patients with and without *BTK* mutations.

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