UPDATED EFFICACY AND SAFETY OF THE BRUTON TYROSINE KINASE (BTK) DEGRADER BGB-16673 IN PATIENTS (PTS) WITH RELAPSED OR REFRACTORY (R/R) CLL/SLL: RESULTS FROM THE ONGOING PHASE (PH) 1 CADANCE-101 STUDY

Authors: Lydia Scarfò,[1,2] Ricardo D. Parrondo,[3] Meghan C. Thompson,[4] Anna Maria Frustaci,[5] John N. Allan,[6] Paolo Ghia,[1,2] Irina Mocanu,[7] Constantine S. Tam,[8] Stephan Stilgenbauer,[9] Damien Roos-Weil,[10] Judith Trotman,[11] Inhye E. Ahn,[12] Nicole Lamanna,[13] Linlin Xu,[14] Kunthel By,[14] Shannon Fabre,[14] Daniel Persky,[14] Amit Agarwal,[14] John F. Seymour[15]

Affiliations: [1]Università Vita-Salute San Raffaele, Milano, Italy; [2]IRCCS Ospedale San Raffaele, Milano, Italy; [3]Mayo Clinic - Jacksonville, Jacksonville, FL, USA; [4]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [5]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [6]Weill Cornell Medicine, New York, NY, USA; [7]Institute of Oncology, ARENSIA Exploratory Medicine, Düsseldorf, Germany; [8]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [9]Ulm University, Ulm, Germany; [10]Pitié-Salpêtrière Hospital, Paris, France; [11]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [12]Dana-Farber Cancer Institute, Boston, MA, USA; [13]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY, USA; [14]BeiGene USA, Inc, San Mateo, CA, USA; [15]Peter MacCallum Cancer Centre, Royal Melbourne Hospital, and University of Melbourne, Melbourne, VIC, Australia

Background: BTK inhibitors (BTKis) are effective treatments (txs) for CLL/SLL, but intolerance and/or acquired resistance due to BTK mutations can emerge. BGB-16673 is a potential first-in-class protein degrader that blocks BTK signaling by tagging BTK for degradation through the cell's proteasome pathway.
Aims: To describe updated ph1 results for pts with R/R CLL/SLL in CaDAnCe-101 (BGB-16673-101; NCT05006716), a ph 1/2 open-label study
Methods: Eligible pts 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/Australia, pts must have previously received a covalent BTKi (cBTKi). BGB-16673 was dosed once daily orally. Primary objectives were to assess safety/tolerability (CTCAE v5.0; iwCLL hematologic toxicity criteria) and establish the maximum tolerated dose and recommended dose for expansion. A secondary objective was to assess ORR (iwCLL 2018 criteria with PR-L modification; 2014 Lugano criteria for SLL).
Results: As of December 17, 2024, 66 pts with CLL/SLL were enrolled and treated (50mg, n=1; 100mg, n=22; 200mg, n=16; 350mg, n=15; 500mg, n=12). Median age was 70 y (range, 47-91); the median number of prior therapies was 4 (range, 2-10), including prior cBTKis (n=61; 92.4%), BCL2 inhibitors (BCL2is; n=54; 81.8%), and noncovalent BTKis (ncBTKis; n=14; 21.2%). In total, 65.2% (43/66) of pts had del(17p) and/or *TP53* mutation and 79.6% (39/49) had unmutated IGHV. Median follow-up was 13.1 mo (range, 0.3-29.9).
Overall, 92.4% of pts had any-grade (gr) tx-emergent AEs (TEAEs; gr ≥3, 51.5%); those in ≥30% of pts were fatigue (36.4%; gr ≥3, 1.5%) and contusion/bruising (30.3%; no gr ≥3). Gr ≥3 TEAEs in ≥10% of pts were neutropenia/neutrophil count decreased (21.2%) and pneumonia (12.1%). Atrial fibrillation (gr 1 in the context of bacterial pneumonia) and febrile neutropenia (in the context of COVID-19 pneumonia and norovirus diarrhea) occurred in 1 pt (1.5%) each. Hypertension (n=2, both gr 3) and major hemorrhage occurred in 2 pts each (3.0%, gr 1 subarachnoid hemorrhage resolved; gr 3 subdural hemorrhage outcome unknown). Six pts (9.1%) had a TEAE leading to dose reduction. Four pts had TEAEs that led to death (pneumonia in the context of disease progression, septic shock, bronchopulmonary & cerebral aspergillosis, and acute respiratory failure; n=1 each); no deaths were deemed related to BGB-16673.

In 66 response-evaluable pts, ORR (PR-L or better) was 80.3% (n=53), and CR/CRi rate was 3.0% (n=2). At 200mg, ORR was 93.8% (15/16), including 1 CR. Median time to first response was 2.8 mo (range, 2.0-10.9). Thirty-three pts (50.0%) remained on tx for ≥12 mo; 38 pts had ongoing responses. Responses deepened over time: of 19 pts with initial PR-L, 10 transitioned to PR and 1 to CR; of 15 pts with initial SD, 1 transitioned to PR-L, 5 to PR, and 1 to CRi. Responses were seen at the lowest dose (50mg, 1/1); in pts previously treated with a cBTKi (49/61; 80.3%) or ncBTKi (10/14; 71.4%) and with double- (cBTKi and BCL2i; 36/41; 87.8%) and triple-exposure (cBTKi, BCL2i, ncBTKi; 9/12; 75.0%); and in pts with (17/24; 70.8%) and without (33/39; 84.6%) *BTK* mutations and with del(17p) and/or *TP53* mutation (33/43; 76.7%). Median PFS was not reached (**Figure**).

Summary/Conclusion: Data from this ongoing study demonstrate that the novel BTK degrader BGB-16673 has a tolerable safety profile and shows robust and deepening responses in pts with heavily pretreated R/R CLL/SLL, including those with prior BTKi tx and BTKi mutations.

Figure. PFS in Patients With R/R CLL