Updated efficacy/safety of the Bruton tyrosine kinase (BTK) degrader BGB-16673 in relapsed/refractory (R/R) CLL/SLL: results from the ongoing phase 1 CaDAnCe-101 study

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ABSTRACT

Introduction: 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. Updated phase (ph) 1 results in R/R CLL/SLL in the ph 1/2 open-label CaDAnCe-101 (BGB-16673-101; NCT05006716) are reported here.

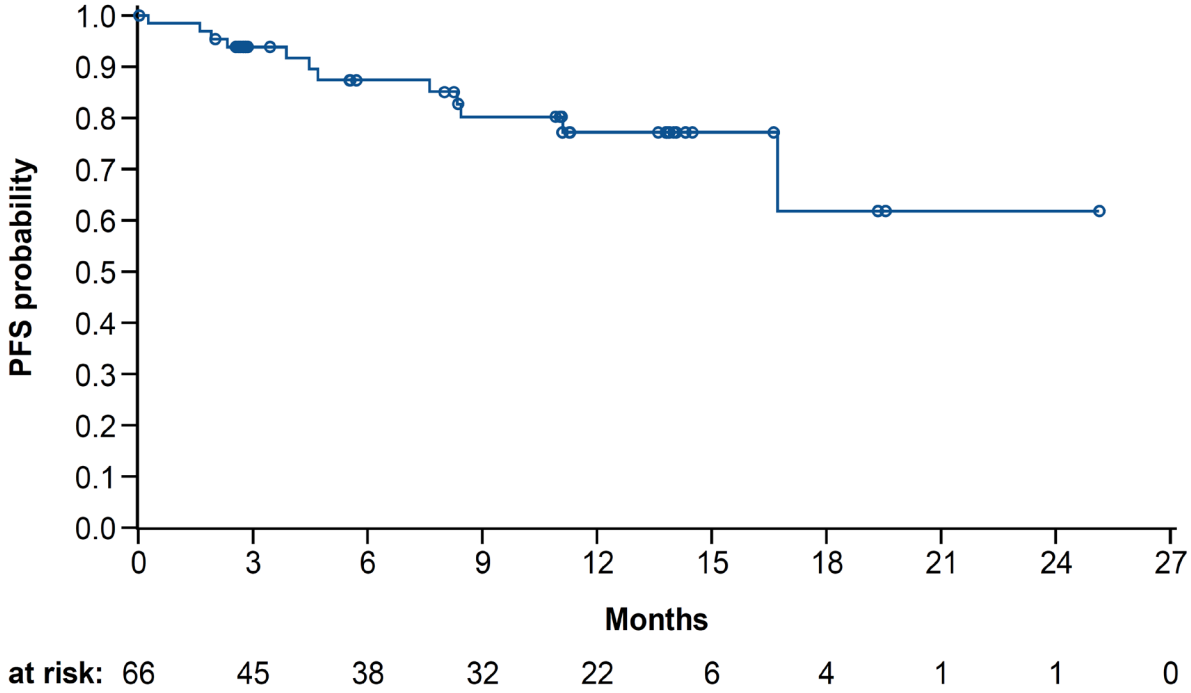
Methods: Patients (pts) with R/R CLL/SLL (≥2 prior therapies including a covalent BTK inhibitor [cBTKi] in US/EU/Australia) received BGB-16673 QD orally. Primary endpoints were safety (CTCAE v5.0; iwCLL hematologic toxicity criteria), MTD, and recommended dose for expansion. A secondary endpoint was ORR (modified iwCLL 2018 criteria; 2014 Lugano criteria for SLL).

Results: As of December 17, 2024, 66 pts with R/R 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); 65.2% of pts (43/66) had del(17p) and/or *TP53* mutation; 79.6% (39/49) had unmutated IGHV. Pts had a median of 4 prior treatments (txs; 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%). Median follow-up was 13.1 mo (range, 0.3-29.9). Tx-emergent AEs (TEAEs) occurred in 92.4% of pts (gr ≥3, 51.5%). TEAEs 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 (gr 1 subarachnoid hemorrhage resolved; gr 3 subdural hemorrhage outcome unknown) occurred in 2 pts (3.0%) each. TEAEs led to dose reduction in 6 pts (9.1%) and death in 4 pts (pneumonia in the context of disease progression, septic shock, bronchopulmonary & cerebral aspergillosis, and acute respiratory failure; n=1 each; none related to tx). In 66 evaluable pts, ORR (PR-L or better) was 80.3% (n=53); CR/CRi rate was 3.0% (n=2). At 200mg, ORR was 93.8% (15/16), with 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 had ongoing responses. 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 occurred in pts with a prior cBTKi (49/61; 80.3%)

or ncBTKi (10/14; 71.4%), double- (cBTKi and BCL2i; 36/41; 87.8%) and triple-exposure (cBTKi, BCL2i, ncBTKi; 9/12; 75.0%), in pts with (17/24; 70.8%) and without (33/39; 84.6%) *BTK* mutations, with del(17p) and/or *TP53* mutation (33/43; 76.7%), and at the lowest dose (50mg, 1/1). Median PFS was not reached (**Figure**).

Conclusions: The novel BTK degrader BGB-16673 has a tolerable safety profile, and robust and deepening responses in pts with heavily pretreated R/R CLL/SLL, including pts with prior BTKis and BTKi mutations.

Figure. PFS in Patients With R/R CLL



No. at risk:	66	45	38	32	22	6	4	1	1	0