Preliminary 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 phase 1 BGB-16673-101 study

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ABSTRACT

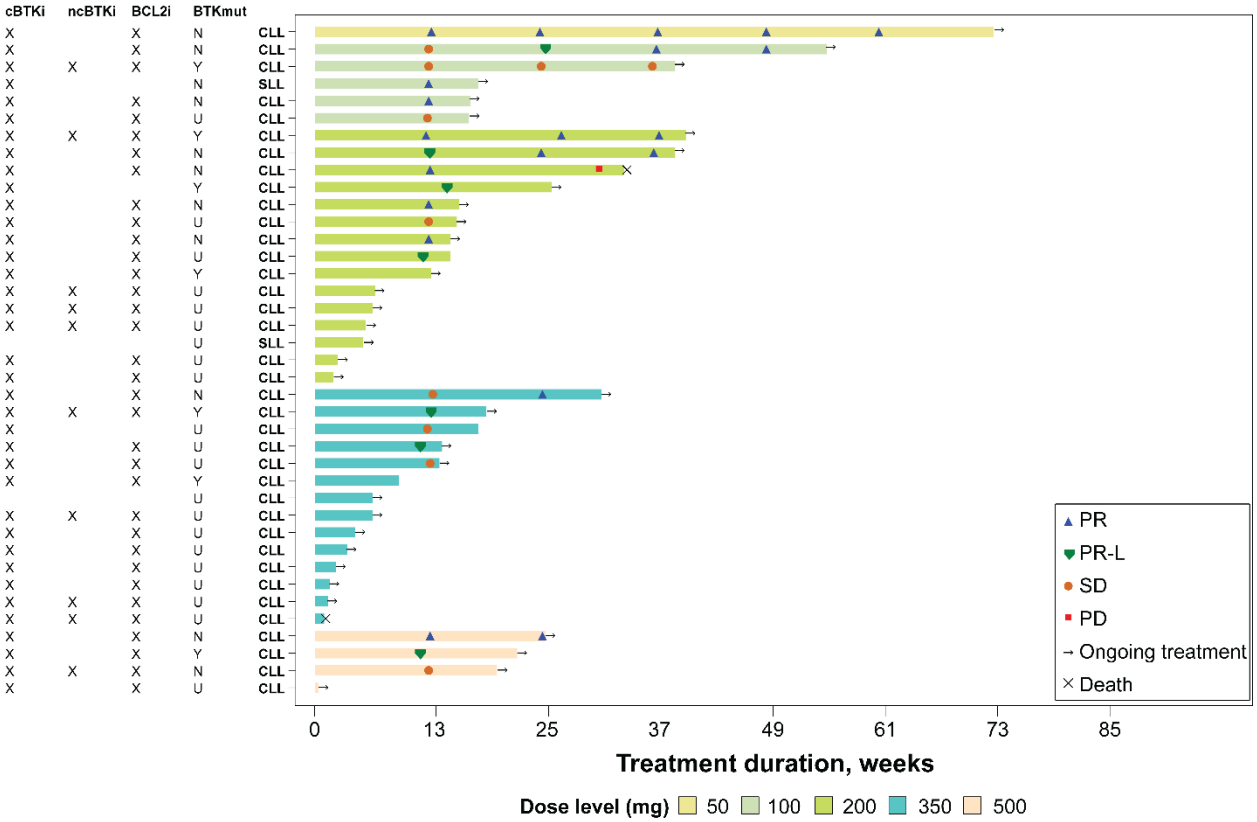
Background: BGB-16673 is a heterobifunctional small molecule that induces BTK degradation via ubiquitination. In preclinical models, BGB-16673 degraded wild-type BTK and BTK-mutant proteins resistant to covalent (cBTKis) and noncovalent BTK inhibitors (ncBTKis), leading to tumor regression. Updated results in pts with CLL/SLL from phase 1 of the first-in-human BGB-16673-101 (NCT05006716) study are presented.

Methods: Eligible pts had CLL/SLL and ≥2 prior therapies, including a cBTKi (US, EU, and Australia). BGB-16673 was dosed QD orally in 28-day cycles. A 6-level dose escalation (50-600 mg QD) was planned. Primary objectives were to assess safety per CTCAE v5.0 and iwCLL hematologic toxicity criteria and establish the maximum tolerated dose (MTD) and recommended phase 2 dose. DLTs were assessed in cycle 1. Response was assessed per iwCLL 2018 criteria (Cheson 2014 for SLL), beginning after 12 wk of treatment.

Results: As of Nov 9, 2023, 42 pts with CLL were enrolled (median age, 70 y; range, 50-91) and 39 were treated (50 mg, n=1; 100 mg, n=5; 200 mg, n=15; 350 mg, n=14; 500 mg, n=4). Pts had a median of 4 (range, 2-8) prior therapies, including cBTKis (n=37; 95%), BCL2 inhibitors (n=34; 87%), and ncBTKis (n=10; 26%). Of tested patients, 54% (20/37) had del(17p) and/or *TP53* mutation, 87% (27/31) had unmutated IGHV, and 43% (12/28) had ≥3 karyotypic abnormalities. Median follow-up was 3.3 mo (range, 0.1-16.7). One DLT occurred (200 mg; grade [gr] 3 maculopapular rash; assigned dose was reinitiated with persistent gr 1 rash). MTD was not reached. The most common TEAEs were contusion (31%; no gr ≥3), fatigue (31%; no gr ≥3), diarrhea (26%; no gr ≥3), and neutropenia (23%; gr ≥3, 18%). One pt (500 mg) had gr 3 hypertension. No atrial fibrillation was observed. TEAEs led to 2 deaths (septic shock and pneumonia, both unrelated to treatment), 2 treatment discontinuations (subdural hemorrhage and thyroid cancer), and 1 dose reduction (gr 2 arthralgia). Thirty-five pts (90%) remain on therapy (discontinuations: 1 progressive disease, 3 AEs). In 24 response-evaluable pts, ORR was 67%, with all but 1 response ongoing. Responses occurred in pts with prior cBTKi (n=16) and ncBTKi (n=2) and in pts with and without BTK mutation (**Figure**).

Conclusions: Emerging data from this ongoing study of the novel BTK degrader BGB-16673 show a tolerable safety profile and antitumor activity in heavily pretreated pts with CLL/SLL, including those with BTK inhibitor–resistant mutations.

Figure. Treatment Duration and Response Assessment in Patients With CLL/SLL



X = patient had the indicated prior therapy; BTK mutation status was classified as present (Y), absent (N), or unknown (U).
cBTKi, covalent BTK inhibitor; mut, mutation; ncBTKi, noncovalent BTK inhibitor; PR-L, PR with lymphocytosis