Preliminary efficacy and safety of the Bruton tyrosine kinase (BTK) degrader BGB-16673 in patients with relapsed or refractory (R/R) CLL/SLL: results from the phase 1 BGB-16673-101 study

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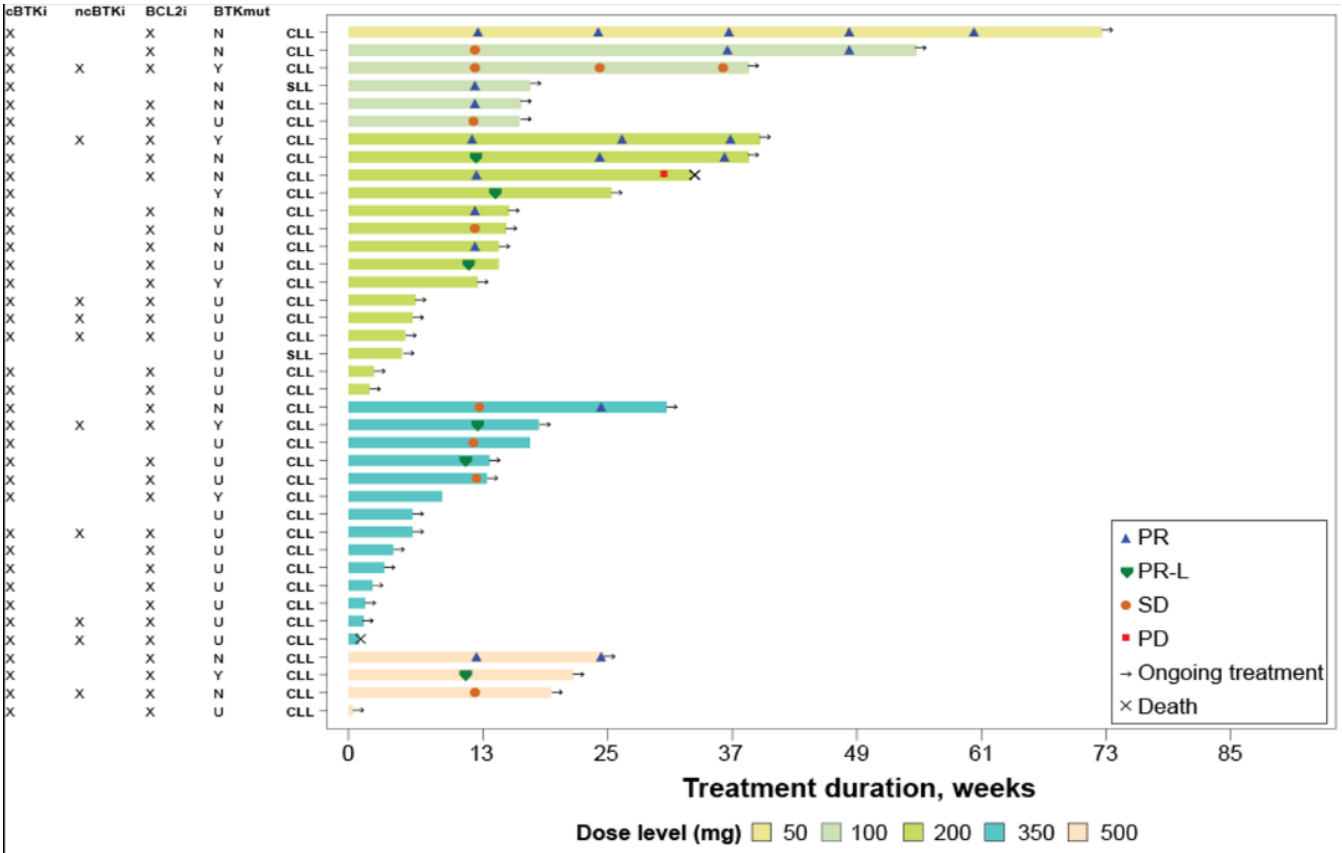
ABSTRACT

Aim: BGB-16673, a heterobifunctional small molecule, induces BTK degradation via ubiquitination. In preclinical models, BGB-16673 degraded wild-type and mutant BTK proteins resistant to covalent (cBTKi) and noncovalent BTK inhibitors (ncBTKi). Updated data for CLL/SLL from the first-in-human study, BGB-16673-101 (NCT05006716), are presented.

Method: Patients had CLL/SLL and ≥2 prior therapies, including cBTKi (US/EU/Australia). BGB-16673 was dosed orally QD in 28-day cycles. Planned dose escalation had 6 levels (50-600mg QD). Primary endpoints included safety (CTCAE v5.0 and iwCLL hematologic toxicity criteria) and maximum tolerated dose (MTD). Dose-limiting toxicity (DLT) was assessed in cycle 1. Response was assessed per iwCLL 2018 criteria (SLL: Cheson 2014).

Results: As of 9Nov2023, 42 patients were enrolled and 39 were treated. Patients had a median of 4 (range, 2-8) prior therapies, including cBTKis (n=37), BCL2 inhibitors (n=34), and ncBTKis (n=10). 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 months (range, 0.1-16.7). One DLT occurred (200mg; grade 3 maculopapular rash). MTD was not reached. The most common treatment-emergent AEs (TEAEs) were contusion (31%; no grade ≥3), fatigue (31%; no grade ≥3), diarrhea (26%; no grade ≥3), and neutropenia (23%; grade ≥3, 18%). One patient (500mg) had grade 3 hypertension. No atrial fibrillation was observed. TEAEs led to 2 deaths (septic shock, pneumonia; each unrelated to treatment), 2 discontinuations (subdural hemorrhage, thyroid cancer), and 1 dose reduction (grade 2 arthralgia). Thirty-five patients (90%) remain on therapy (discontinuations: 1 progressive disease; 3 AE). In 24 response-evaluable patients, ORR was 67%, with 23/24 responses ongoing, including in patients with prior cBTKi (n=16) and ncBTKi (n=2), and with and without BTK mutation (Figure).

Conclusion: BGB-16673 demonstrated preliminary tolerability and antitumor activity in heavily pretreated patients with CLL/SLL, including those with BTK inhibitor-resistant mutations.



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