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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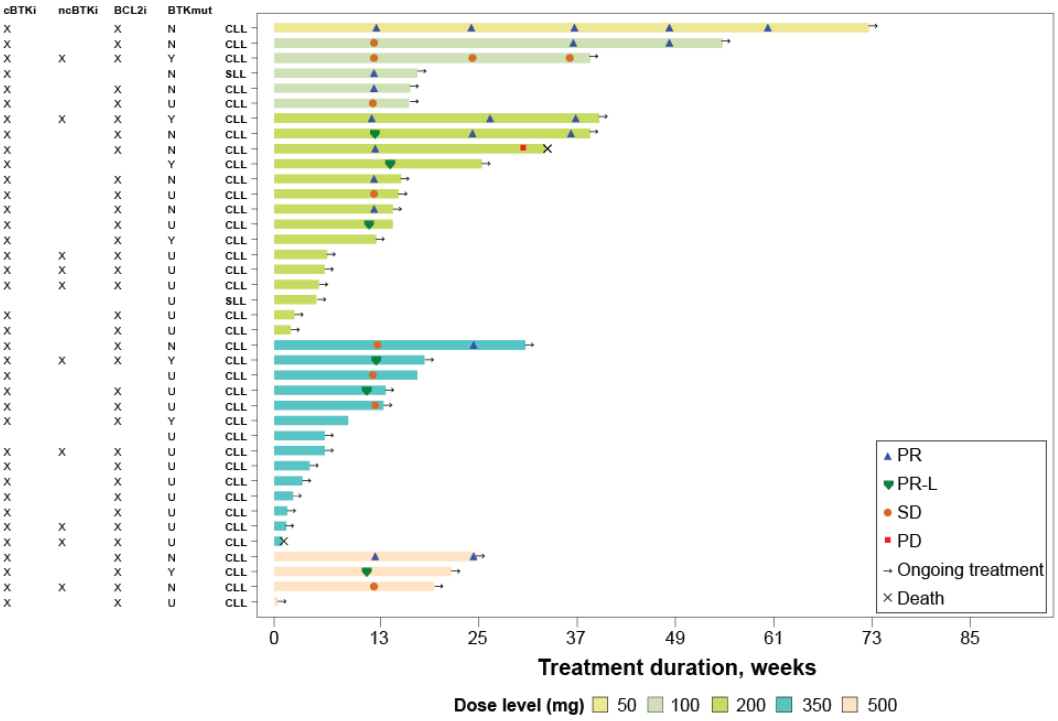
ABSTRACT

Introduction: 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 data from BGB-16673-101 (NCT05006716), a first-in-human study of BGB-16673, are presented for CLL/SLL.

Methods: Eligible pts had ≥2 prior therapies, including a cBTKi (US, EU, and Australia). BGB-16673 was dosed QD orally in 28-d cycles; dose escalation (50-600mg QD) was planned. Primary endpoints were safety per CTCAE v5.0 and iwCLL hematologic toxicity criteria, maximum tolerated dose (MTD), and recommended phase 2 dose. DLTs were assessed in cycle 1. Response was assessed (iwCLL 2018 or Cheson 2014) after 12 wk of treatment (tx).

Results: As of Nov 9, 2023, 42 pts were enrolled; 39 were treated (50mg, n=1; 100mg, n=5; 200mg, n=15; 350mg, n=14; 500mg, n=4). Pts had a median of 4 (range, 2-8) prior therapies, including cBTKis (95%), BCL2 inhibitors (87%), and ncBTKis (26%). Of tested pts, 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 (200mg; gr 3 maculopapular 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), neutropenia (23%; gr ≥3, 18%). One pt (500mg) had gr 3 hypertension. No atrial fibrillation was observed. TEAEs led to 2 deaths (septic shock and pneumonia; both unrelated to tx), 2 tx discontinuations (subdural hemorrhage and thyroid cancer), and 1 dose reduction (gr 2 arthralgia). Thirty-five pts (90%) remain on therapy (discontinuations: 1 progression, 3 AEs). In 24 evaluable pts, ORR was 67%, with all but 1 response ongoing. Responses were seen with prior cBTKi (n=16) and ncBTKi (n=2), and with and without BTK mutation (**Figure**).

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



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