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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Background: BTK inhibitors are approved for CLL, but intolerability and treatment resistance can limit their use. BGB-16673 is a heterobifunctional small molecule that induces BTK degradation via ubiquitination. In preclinical models, BGB-16673 degraded wild-type and mutant BTK proteins resistant to covalent (cBTKis) and noncovalent BTK inhibitors (ncBTKis), leading to tumor regression. BGB-16673 is currently being evaluated in phase 1 studies. Updated results from patients with CLL/SLL in the phase 1 portion of the open-label first-in-human, BGB-16673-101 study (NCT05006716) are presented.

Material and Methods: Eligible patients must have R/R CLL/SLL (≥2 prior therapies), an ECOG performance status of 0-2, and adequate end-organ function. In the US, EU, and Australia, patients must have previously received a cBTKi. BGB-16673 was dosed once daily orally in 28-day cycles. Dose escalation using a Bayesian optimal interval design with 6 dose levels (50-600 mg once daily) was planned. Primary objectives were to assess safety/tolerability per CTCAE v5.0 and iwCLL hematologic toxicity criteria and establish the maximum tolerated dose (MTD) and recommended phase 2 dose. Dose-limiting toxicities (DLTs) were assessed in the first 4 weeks (cycle 1). Response was assessed per iwCLL 2018 criteria (or Cheson et al, 2014 for SLL), with first assessment after 12 weeks of treatment.

Results: As of November 9, 2023, 42 patients with CLL were enrolled (median age, 70 years; 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). Treated patients had a median of 4 prior therapies (range, 2-8), 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 time was 3.3 months (range, 0.1-16.7). One DLT occurred in 1 patient (200 mg; grade 3 maculopapular rash on day 27; after 5-day dose hold, assigned dose was reinitiated with persistent grade 1 rash). MTD was not reached. The most common 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 (500 mg) had a TEAE of grade 3 hypertension. No atrial fibrillation was observed. TEAEs led to death in 2 patients (septic shock and pneumonia; neither was considered related to treatment), treatment discontinuation in 2 additional patients (subdural hemorrhage and thyroid cancer), and dose reduction in 1 patient (grade 2 arthralgia). Thirty-five of 39 patients (90%) remain on therapy (4 discontinuations: progressive disease, n=1; AEs, n=3). For 24 response-evaluable patients, the ORR was 67%, with all but 1 response ongoing. Responses were seen at the lowest dose, in patients previously treated with cBTKi (n=16) and ncBTKi (n=2), and in patients with and without BTK mutation.

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