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

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ABSTRACT

Objective: Bruton tyrosine kinase (BTK) inhibitors are approved for chronic lymphocytic leukemia (CLL), but intolerability and treatment resistance can limit their use. There is a clinical need for novel CLL treatments following progression after treatment with current standard of care therapies, including BTK inhibitors. BGB-16673 is a heterobifunctional small molecule that induces BTK degradation via ubiquitination and was designed to avoid IMiD activity. In preclinical models, BGB-16673 degraded wild-type BTK and known covalent and noncovalent BTK inhibitor-resistant mutant proteins, leading to tumor regression. BGB-16673 is currently being evaluated in phase 1 studies. Updated results from patients with CLL/small lymphocytic lymphoma (SLL) enrolled in the phase 1 portion of the open-label, first-in-human, BGB-16673-101 (NCT05006716) study are reported.

Methods: Eligible patients must have relapsed or refractory (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 covalent BTK inhibitor. 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 and establish the maximum tolerated dose (MTD) and recommended phase 2 dose. Safety was assessed per CTCAE v5.0 and iwCLL hematologic toxicity criteria. 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 09 November 2023, 42 patients with CLL were enrolled (median age, 70 years [range, 50-91 years]) and 39 patients were treated (50 mg [n=1]; 100 mg [n=5]; 200 mg, [n=15]; 350 mg, [n=14]; 500 mg, [n=4]). For treated patients, the median number of prior therapies was 4 (range, 2-8), including cBTKis (n=37; 95%), BCL2 inhibitors (n=34; 87%), and noncovalent BTK inhibitors (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. The median follow-up time was 3.3 months (range, 0.1-16.7 months). One DLT occurred in 1 patient at 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. Two patients had TEAEs that led to death (septic shock and pneumonia); neither was considered related to treatment. Two additional patients had TEAEs that led to treatment discontinuation (subdural hemorrhage and thyroid cancer). One patient had a dose reduction due to 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 a covalent BTK inhibitor (n=16) and a noncovalent BTK inhibitor (n=2), and in patients with and without BTK mutation.

Conclusion: 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.