Preliminary efficacy and safety of the Bruton tyrosine kinase degrader BGB-16673 in patients with relapsed or refractory indolent non-Hodgkin lymphoma: results from the phase 1 BGB-16673-101 study

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ABSTRACT

Objective: Bruton tyrosine kinase (BTK) inhibitors have significantly advanced the treatment of B-cell malignancies; however, treatment resistance often emerges and is sometimes associated with emergence of BTK mutations. 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 being assessed across B-cell malignancies, including follicular lymphoma (FL), marginal zone lymphoma (MZL), and Waldenstrom macroglobulinemia (WM). Here, updated results from patients with FL, MZL, and WM enrolled in the phase 1 portion of the open-label, first-in-human trial, BGB-16673-101 (NCT05006716) are reported.

Methods: Eligible patients must have relapsed or refractory (R/R) non-Hodgkin lymphoma (≥2 prior therapies), an ECOG performance status of 0-2, and adequate end-organ function. In the US and EU, patients with WM and MZL must have previously received a CD20 antibody; US patients with WM 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. Dose-limiting toxicities (DLTs) were assessed in the first 4 weeks (cycle 1). Response was assessed per 2014 Lugano Classification or IWWM consensus criteria, with first assessment after 4 weeks (WM) or 12 weeks (FL and MZL) of treatment.

Results: As of 09 November 2023, 24 patients with FL (n=7), MZL (n=4), and WM (n=13) were enrolled (median age, 72 years [range, 56-79]). Twenty-three patients have been treated (100 mg [n=5]; 200 mg, [n=11]; 350 mg, [n=7]) and 1 patient with WM had not yet started treatment. For treated patients, the median number of prior therapies was 4 (FL and WM) and 2 (MZL), including covalent BTK inhibitors (14/23), BCL2 inhibitors (5/23), and noncovalent BTK inhibitors (3/23). The median follow-up times were 6.6, 5.9, and 1.9 months for FL, MZL, and WM, respectively. TEAEs occurring in >10% of patients were

contusion (22%), fatigue (22%), amylase increased (17%), headache (13%), lipase increased (13%), neutropenia (13%), and upper respiratory tract infection (13%). Neutropenia was the only grade ≥3 event in >1 patient (n=2). No events of hypertension or atrial fibrillation occurred. One patient with WM (350 mg) had a TEAE that led to treatment discontinuation (bronchopulmonary aspergillosis; subsequent investigation showed presence prior to treatment). One patient with WM (200 mg) experienced a TEAE that led to death (septic shock, in the context of disease progression, not related to treatment). No patients had a TEAE that led to dose reduction. No DLTs occurred. Seventeen of 23 patients remain on therapy (discontinuations: 4 progressive disease, 1 AE, 1 patient withdrawal). For 14 response-evaluable patients, the ORR was 50% (2/4) for FL, 100% (2/2) for MZL, and 75% (6/8) for WM, which included patients who received a covalent BTK inhibitor (n=7; 6 WM, 1 MZL) and a noncovalent BTK inhibitor (n=2).

Conclusion: Preliminary 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 non-Hodgkin lymphoma, including those with BTK inhibitor-resistant disease.