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

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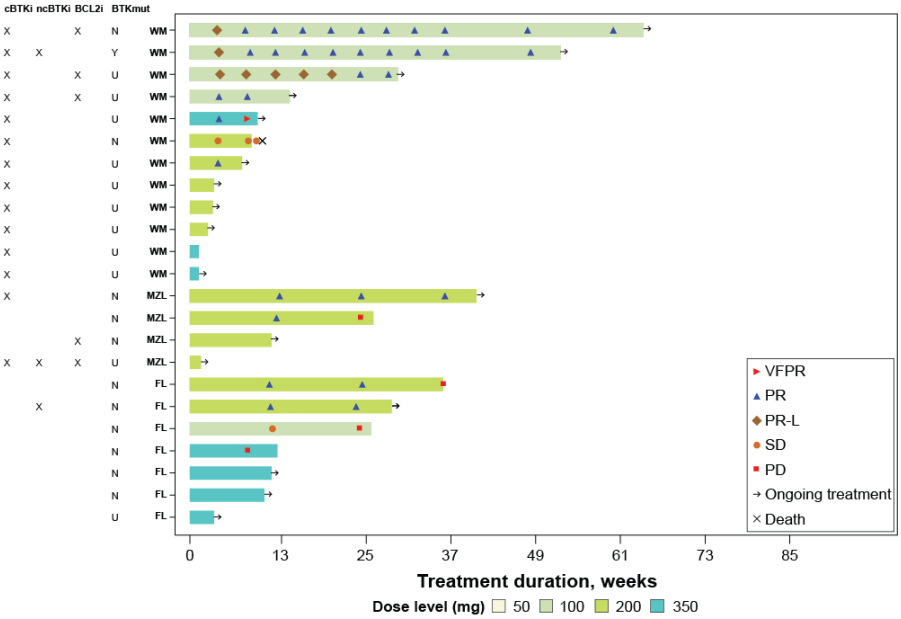
ABSTRACT

Introduction: BGB-16673 is a heterobifunctional small molecule that induces BTK degradation via ubiquitination. In preclinical models, BGB-16673 degraded wild-type BTK and mutants 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 pts with follicular lymphoma (FL), marginal zone lymphoma (MZL), and Waldenstrom macroglobulinemia (WM).

Methods: Pts had R/R NHL and ≥2 prior therapies, including anti-CD20 (FL/WM/MZL in US/EU) and cBTKi (WM in US/EU; MZL in US). BGB-16673 was dosed QD orally in 28-day cycles; dose escalation (50-600mg QD) was planned. Primary endpoints were safety per CTCAE v5.0, maximum tolerated dose, and recommended phase 2 dose. DLTs were assessed in cycle 1. Response assessment per 2014 Lugano classification or IWWM-6 criteria began after 4 (WM) or 12 wk (FL and MZL) of treatment.

Results: As of Nov 9, 2023, 24 pts (FL, n=7; MZL, n=4; WM, n=13) were enrolled and 23 started treatment (100mg, n=5; 200mg, n=11; 350mg, n=7). Pts had a median of 4 (FL and WM) and 2 (MZL) prior therapies, including cBTKis (14/23), BCL2 inhibitors (5/23), and ncBTKis (3/23). Median follow-up was 6.6, 5.9, and 1.9 mo in FL, MZL, and WM, respectively. TEAEs in >15% were contusion (22%), fatigue (22%), and amylase increased (17%). Neutropenia was the only grade ≥3 event in >1 pt (n=2). No hypertension or atrial fibrillation occurred. TEAEs led to 1 treatment discontinuation (WM; 350mg; bronchopulmonary aspergillosis; present pretreatment) and 1 death (WM; 200mg; septic shock; not treatment related). No TEAEs led to dose reduction. No DLTs occurred. Of 23 pts, 17 remain on treatment (discontinuations: 4 progression, 1 AE, 1 withdrawal). In 14 response-evaluable pts, ORR was 50% (2/4) in FL, 100% (2/2) in MZL, and 75% (6/8) in WM, including pts with prior cBTKi (n=7; 6 WM, 1 MZL) and ncBTKi (n=2; **Figure**).

Conclusions: Preliminary data from this ongoing study of BTK degrader BGB-16673 demonstrate a tolerable safety profile and antitumor activity in heavily pretreated pts with NHL, 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; FL, follicular lymphoma; MR, minor response; mut, mutation; MZL, marginal zone lymphoma; ncBTKi, noncovalent BTK inhibitor; VGPR, very good PR; WM, Waldenström macroglobulinemia.