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

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ABSTRACT

Background: BGB-16673 is a heterobifunctional small molecule that induces BTK degradation via ubiquitination. In preclinical models, BGB-16673 degraded wild-type BTK and BTK mutants resistant to covalent (cBTKis) and noncovalent BTK inhibitors (ncBTKis), leading to tumor regression. BGB-16673-101 (NCT05006716) is a first-in-human phase 1 study of BGB-16673 in pts with B-cell malignancies. Updated data from pts with follicular lymphoma (FL), marginal zone lymphoma (MZL), and Waldenstrom macroglobulinemia (WM) will be presented.

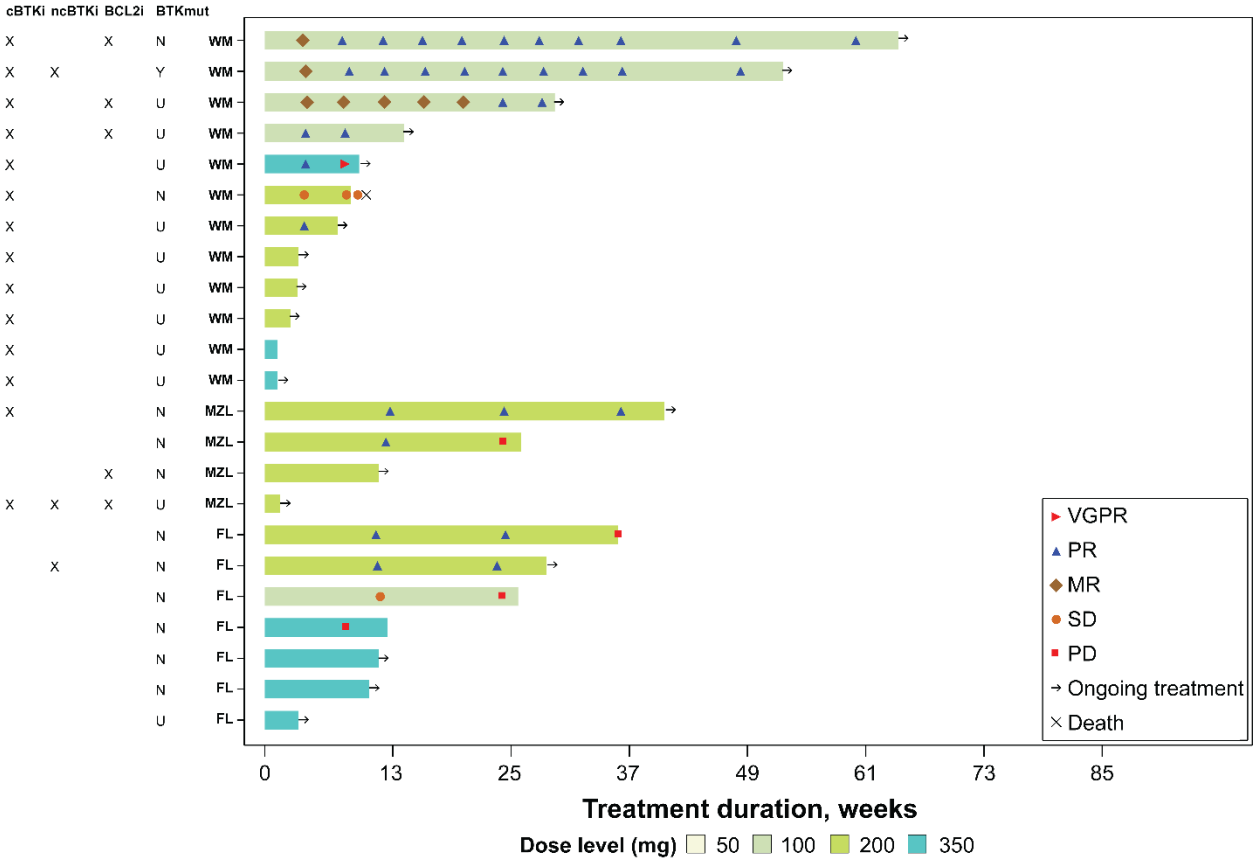
Methods: Eligible pts had R/R NHL and ≥2 prior therapies, including prior anti-CD20 (FL, WM, and MZL in US and EU) and cBTKi (WM in US and EU; MZL in US). BGB-16673 was dosed QD orally in 28-day cycles. Dose escalation with 6 dose levels (50-600 mg QD) was planned. Primary objectives were to assess safety per CTCAE v5.0 and establish the maximum tolerated dose (MTD) 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 (tx).

Results: As of Nov 9, 2023, 24 pts (FL, n=7; MZL, n=4; WM, n=13) were enrolled and 23 were treated (100 mg, n=5; 200 mg, n=11; 350 mg, n=7); 1 pt with WM had not started tx. 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 >10% of pts 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 pt (n=2). No hypertension or atrial fibrillation occurred. TEAEs led to tx discontinuation in 1 pt with WM (350 mg; bronchopulmonary aspergillosis; present prior to tx) and death in 1 pt with WM (200 mg; septic shock; not tx related). No TEAEs led to dose reduction. No DLTs occurred. Of 23 pts, 17 remain on tx (discontinuations: progressive disease, n=4; AE, n=1; pt withdrawal, n=1). 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 those with

BTK inhibitor–resistant disease.

Figure. Treatment Duration and Response Assessment in Patients With FL, MZL, or WM



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.