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POSTER ABSTRACTS

623.MANTLE CELL, FOLLICULAR, AND OTHER INDOLENT B CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

First Results from a Phase 1, First-in-Human Study of the Bruton's Tyrosine Kinase (BTK) Degrader Bgb-16673 in Patients (Pts) with Relapsed or Refractory (R/R) B-Cell Malignancies (BGB-16673-101)

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Introduction: BTK inhibitors (BTKis) are approved for chronic lymphocytic leukemia (CLL), Waldenström macroglobulinemia (WM), mantle cell lymphoma (MCL), and marginal zone lymphoma (MZL). Disease that progresses on BTKis often has BTK mutations that lead to treatment (tx) resistance; novel BTK-targeting agents that overcome BTKi resistance are needed. BGB-16673 is a heterobifunctional small molecule that binds to BTK and E3 ligase, resulting in BTK degradation via ubiquitination. In preclinical models, BGB-16673 degraded wild-type (WT) BTK and known covalent and noncovalent BTKi-resistant mutant proteins, leading to tumor suppression.
Methods: Pts with R/R CLL, WM, MCL, MZL, non-germinal center B-cell diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), or Richter transformation (RT) were eligible for this open-label, first-in-human, phase 1 trial (BGB-16673-101; NCT05006716). Pts must have received ≥2 prior therapies (≥1 for RT) and have an ECOG performance status of 0-2 and adequate end-organ function. In the US and Australia, pts must have received a covalent BTKi (cBTKi) if approved for their disease. BGB-16673 was dosed daily by mouth in 28-day cycles. Escalation using a Bayesian optimal interval design with 6 dose levels (50-600 mg once daily) is planned. Primary objectives are to assess safety/tolerability and establish the maximum tolerated dose (MTD) and recommended phase 2 dose. Key secondary objectives are to assess pharmacokinetics, pharmacodynamics (PD), and preliminary antitumor activity. Safety was assessed according to CTCAE v5.0 (all pts) and iwCLL hematologic toxicity criteria (pts with CLL). Dose-limiting toxicities (DLTs) were assessed in the first 4 weeks. Response was assessed per Lugano criteria for all except CLL (iwCLL 2018 criteria) and WM (iwWM-6 criteria).
Results: As of May 26, 2023, 26 pts (10 CLL, 4 MCL, 2 MZL, 4 WM, 4 FL, 1 DLBCL, 1 RT) were enrolled at 5 dose levels (50 mg, 4; 100 mg, 9; 200 mg, 9; 350 mg, 3; 500 mg, 1). Median age was 70.5 y (range, 25-83). Median number of prior therapies was 3.5 (range, 2-9), including cBTKis (n=21; 10 CLL, 4 WM, 4 MCL, 1 MZL, 1 RT, 1 DLBCL), BCL2 inhibitors (n=12; 9 CLL, 2 WM,

1 RT), and noncovalent BTKis (ncBTKis; n=4; 2 CLL, 1 WM, 1 FL). In CLL, del17p/ *TP53* mutation (n=8) and unmutated IGHV (n=7) were frequent.

Median follow-up was 3.5 mo (range, 0.2-13.9). MTD was not reached. Treatment-emergent AEs (TEAEs) were reported by 88.5% of pts (grade [gr] ≥3, 46.2%; serious, 38.5%). The most common TEAEs were contusion (30.8%; no gr ≥3), pyrexia (23.1%; no gr ≥3), neutropenia/neutrophil count decreased (23.1%; gr ≥3, 15.4%), and lipase increased (23.1%; gr ≥3, 3.8%; all transient and asymptomatic). No hypertension or atrial fibrillation was observed. One pt died from sepsis with possible disease progression. No discontinuations due to AEs occurred. Two pts had dose reductions due to TEAEs (gr 3 hematuria with urinary tract infection and recurrent urothelial carcinoma and gr 2 arthralgia). One DLT occurred in 1 pt at 200 mg (gr 3 maculopapular rash on day 27; after 5-day dose hold, assigned dose was recommenced with persistent gr 1 rash).

BGB-16673 exposure increased in a dose-dependent manner. At steady state with doses ≥50 mg daily, BGB-16673 exposure exceeded the calculated half maximal degradation concentration for WT and cysteine 481-mutated BTK for the dosing interval. Preliminary PD data showed deep, sustained reductions in BTK protein levels in peripheral blood and tumor tissue, even at the lowest dose. Most CLL pts experienced lymphocytosis during the first 3 cycles of tx. Twenty of 26 pts (77%) remain on therapy (discontinuation: 4 progressive disease, 2 withdrawal). Of 18 response-evaluable pts, 12 (67%) responded (5/6 CLL, 1/3 MCL, 2/2 MZL, 3/4 WM, 1/2 FL, 0/1 DLBCL; 1 CR in MCL, all others had PR; *Figure*), including pts who received a cBTKi (n=10) and an ncBTKi (n=2). Responses started at the lowest dose level. All responders remain in response, the longest responder remaining on tx for 60 weeks.

Conclusions: Preliminary data from this ongoing, first-in-human study of the novel BTK degrader BGB-16673 demonstrate a tolerable safety profile and clinical responses in heavily pretreated pts with B-cell malignancies, including those with BTKi-resistant disease. Substantial reductions in BTK protein levels in peripheral blood and tumor tissue were also observed, demonstrating proof-of-concept of a strong, on-target effect.

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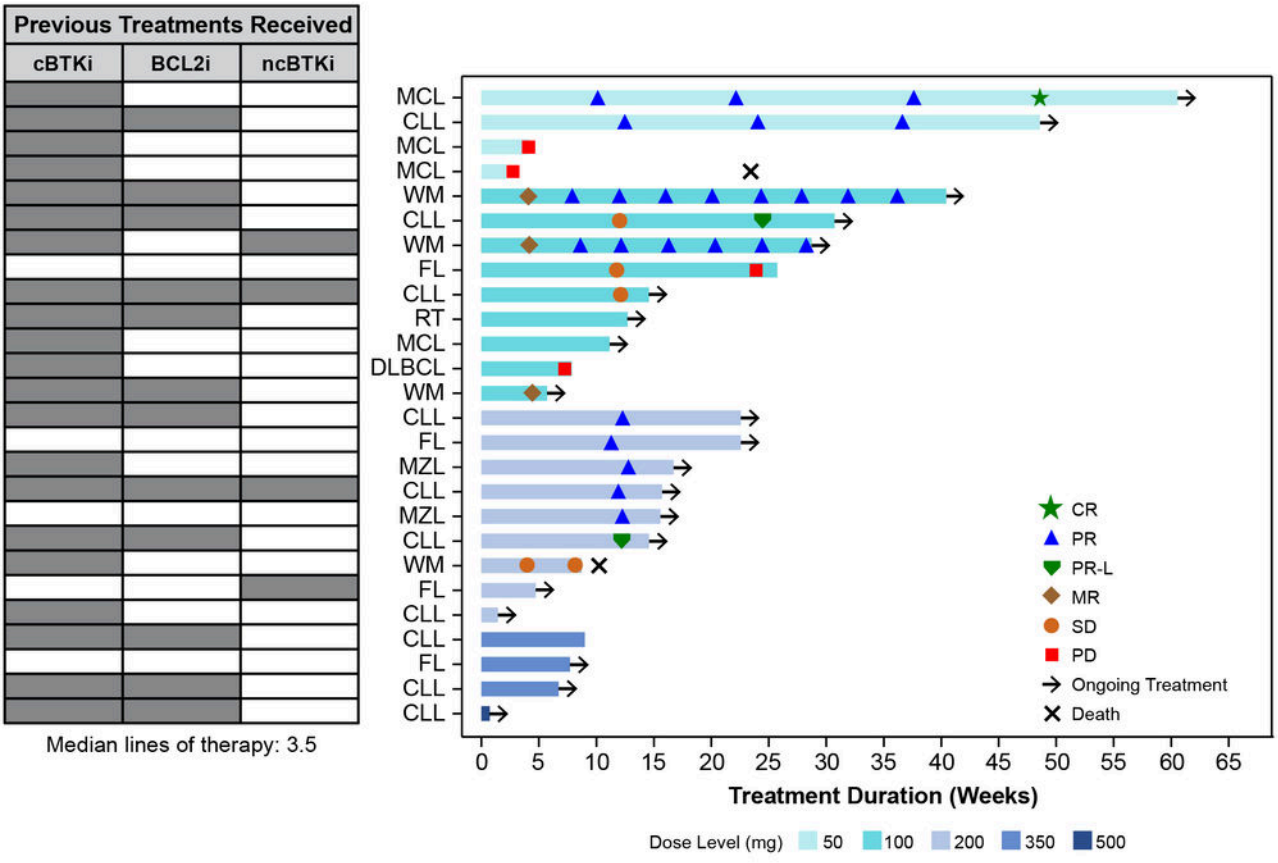
Figure. Patient Response to BGB-16673 Treatment by Dose-Level and B-Cell Malignancy



BCL2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; cBTKi, covalent BTKi; CLL, chronic lymphocytic leukemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MR, minor response; MZL, marginal zone lymphoma; ncBTKi, non-covalent BTKi; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; RT, Richter transformation; SD, stable disease; WM, Waldenström macroglobulinemia.

Figure 1

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