First results from a phase 1, first-in-human study BGB-16673 in patients with relapsed/refractory B-cell malignancies

Authors: Talha Munir,[1] Chan Y. Cheah,[2-4] Ricardo Parrondo,[5] Meghan C. Thompson,[6] Kunthel By,[7] Xiangmei Chen,[7] Shannon Fabre,[7] Jason Paik,[7] Constantine S. Tam,[8] John F. Seymour[9]

Affiliations: [1]Leeds Teaching Hospitals NHS Trust, Leeds, UK; [2]Department of Haematology, Sir Charles Gairdner Hospital and Pathwest Laboratory Medicine, Nedlands, WA, Australia; [3]Medical School, University of Western Australia, Crawley, WA, Australia; [4]Linear Clinical Research, Nedlands, WA, Australia; [5]Mayo Clinic-Jacksonville, Jacksonville, FL, USA; [6]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [7]BeiGene (Shanghai) Co, Ltd, Shanghai, China, and BeiGene USA, Inc, San Mateo, CA, USA; [8]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [9]Peter MacCallum Cancer Centre, Royal Melbourne Hospital, and University of Melbourne, Melbourne, VIC, Australia

ABSTRACT

Introduction: B-cell malignancies that progress on BTK inhibitors (BTKis) often have BTK mutations associated with treatment resistance. BGB-16673 is a heterobifunctional small molecule that binds BTK and E3 ligase, resulting in BTK degradation via ubiquitination. In preclinical models, BGB-16673 degraded wild-type BTK and known covalent and noncovalent BTKi-resistant mutant proteins, leading to tumor suppression.

Methods: In BGB-16673-101 (NCT05006716), eligible patients had B-cell malignancies treated with ≥2 prior therapies (≥1, Richter transformation), including, if approved for their disease, a covalent BTKi (cBTKi). BGB-16673 was administered orally, once daily, in 28-day cycles at 5 planned dose levels. The primary objectives are to assess safety/tolerability and establish the maximum tolerated dose (MTD) and recommended phase 2 dose. Secondary objectives include evaluation of pharmacokinetics, pharmacodynamics, dose-limiting toxicities (DLTs), and antitumor activity. Responses are assessed per Lugano criteria, except for CLL (iwCLL 2018 criteria) and WM (iwWM-6 criteria).

Results: As of 26May2023, 26 patients were enrolled (50mg, n=4; 100mg, n=9; 200mg, n=9; 350mg, n=3; 500mg, n=1) with a median of 3.5 prior therapies (range, 2-9), including cBTKis (n=21), BCL2 inhibitors (n=12), and noncovalent BTKis (ncBTKis; n=4). del(17p)/*TP53* mutation (n=8) and unmutated IGHV (n=7) were frequent in CLL. Median follow-up was 3.5 months (range, 0.2-13.9). MTD was not reached. Treatment-emergent AEs (TEAEs) occurred in 88.5% of patients (grade ≥3, 46.2%; serious, 38.5%); the most common were contusion (30.8%; no grade ≥3), pyrexia (23.1%; no grade ≥3), neutropenia/neutrophil count decreased (23.1%; grade ≥3, 15.4%), and lipase increased (23.1%; grade ≥3, 3.8%). No hypertension or atrial fibrillation were observed. One patient died (sepsis with possible disease progression). No discontinuations due to AEs occurred. Two patients had dose reductions due to TEAEs (grade 3 hematuria; grade 2 arthralgia). One DLT occurred (200mg; grade 3 maculopapular rash). BGB-16673 exposure increased dose dependently. At steady state with doses ≥50 mg daily, BGB-16673 exposure exceeded the calculated half-maximal degradation concentration for WT and C481-mutated BTK for the dosing interval. Preliminary data showed reduced BTK protein levels in peripheral blood and tumor tissue. Most patients with CLL experienced lymphocytosis during the first 3 cycles. Twenty patients (77%) remain on therapy (discontinuations: 4 progressive disease; 2 withdrawal). Of 18 response-evaluable patients, 67% responded (1 CR), including patients with prior cBTKi (n=10) and ncBTKi (n=2).

Conclusions: Preliminary data from this ongoing, first-in-human study of BGB-16673 demonstrate a tolerable safety profile and meaningful clinical responses in heavily pretreated patients with B-cell malignancies, including BTKi-resistant disease.