

## First results from a phase 1, first-in-human study of the bruton tyrosine kinase degrader BGB-16673 in patients with relapsed/refractory B-cell malignancies

**Authors:** Romain Guièze,<sup>1</sup> John F. Seymour,<sup>2</sup> Chan Y. Cheah,<sup>3-5</sup> Ricardo Parrondo,<sup>6</sup> Meghan C. Thompson,<sup>7</sup> Don Stevens,<sup>8</sup> Masa Lasica,<sup>9</sup> Michael Wang,<sup>10</sup> Abhijeet Kumar,<sup>11</sup> Judith Trotman,<sup>12</sup> Maan Alwan,<sup>13</sup> Wei Ding,<sup>14</sup> Kunthel By,<sup>15</sup> Bilal Tariq,<sup>15</sup> Xiangmei Chen,<sup>15</sup> Shannon Fabre,<sup>15</sup> Jason Paik,<sup>15</sup> Amit Agarwal,<sup>15</sup> and Constantine S. Tam<sup>16,17</sup>

**Affiliations:** <sup>1</sup>Department of Hematology and Cell Therapy, Estaing University Hospital, Clermont-Ferrand, France <sup>2</sup>Peter MacCallum Cancer Centre, Royal Melbourne Hospital, and University of Melbourne, Melbourne, VIC, Australia; <sup>3</sup>Department of Haematology, Sir Charles Gairdner Hospital and Pathwest Laboratory Medicine, Nedlands, WA, Australia; <sup>4</sup>Medical School, University of Western Australia, Crawley, WA, Australia; <sup>5</sup>Linear Clinical Research, Nedlands, WA, Australia; <sup>6</sup>Mayo Clinic-Jacksonville, Jacksonville, FL, USA; <sup>7</sup>Memorial Sloan Kettering Cancer Center, New York, NY, USA; <sup>8</sup>Norton Healthcare, Louisville, KY, USA; <sup>9</sup>St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; <sup>10</sup>MD Anderson Cancer Center, Houston, TX, USA; <sup>11</sup>University of Arizona College of Medicine – Tucson, Tucson, AZ, USA; <sup>12</sup>Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; <sup>13</sup>Perth Blood Institute, West Perth, WA, Australia; <sup>14</sup>Mayo Clinic-Rochester, Rochester, MN, USA; <sup>15</sup>BeiGene (Shanghai) Co, Ltd, Shanghai, China, and BeiGene USA, Inc, San Mateo, CA, USA; <sup>16</sup>Alfred Hospital, Melbourne, VIC, Australia; and <sup>17</sup>Monash University, Clayton, 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  $\geq 2$  prior therapies ( $\geq 1$ , 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  $\geq 3$ , 46.2%; serious, 38.5%); the most common were contusion (30.8%; no grade  $\geq 3$ ), pyrexia (23.1%; no grade  $\geq 3$ ), neutropenia/neutrophil count decreased (23.1%; grade  $\geq 3$ , 15.4%), and lipase increased (23.1%; grade  $\geq 3$ , 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  $\geq 50$  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.