A Phase 1 Study With the Novel B-Cell Lymphoma 2 Inhibitor BGB-11417 as Monotherapy or in Combination With Zanubrutinib in Patients With B-Cell Malignancies: Preliminary Data

Jacob D. Soumerai MD[1], Stephen Opat MBBS (Hons), FRACP, FRCPA[2,3], Chan Y. Cheah MBBS, FRACP, FRCPA, DMedSc[4,5,6], Masa Lasica MBBS, FRACP, FRCPA[7], Emma Verner MBBS, BMedSci, FRCPA, FRACP[8,9], Peter J. Browett BMedSci, MBChB, FRACP, FRCPA[10], Henry Chan MD[11], Eva González Barca MD[12], James Hilger PhD[13], Yiqian Fang PhD[13], David Simpson MBChB, FRACP, FRCPA[13], Constantine S. Tam MBBS, MD[14,15,16]
[1]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, USA. [2]Monash Health, Clayton, Australia. [3]Monash University, Clayton, Australia. [4]Sir Charles Gairdner Hospital and Pathwest Laboratory Medicine, Nedlands, Australia. [5]Medical School, University of Western Australia, Crawley, Australia. [6]Linear Clinical Research, Nedlands, Australia. [7]St Vincent's Hospital Melbourne, Fitzroy, Australia. [8]Concord Repatriation General Hospital, Concord, Australia. [9]University of Sydney, Sydney, Australia. [10]Auckland City Hospital, Auckland, New Zealand. [11]North Shore Hospital Auckland, Auckland, New Zealand. [12]Institut Català d'Oncologia Hospitalet, IDIBELL, Universitat de Barcelona, Barcelona, Spain. [13]BeiGene USA, Inc., San Mateo, USA. [14]Peter MacCallum Cancer Centre, Melbourne, Australia. [15]University of Melbourne, Parkville, Australia. [16]Royal Melbourne Hospital, Parkville, Australia

Abstract

Context: B-cell lymphoma 2 (BCL2) is aberrantly expressed in many hematologic malignancies and promotes tumorigenesis. BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, phase 1/1b dose-escalation/expansion study evaluating the safety, tolerability, maximum tolerated dose (MTD), and recommended phase 2 dose of oral BGB-11417, a potent, highly selective BCL2 inhibitor, alone or in combination with zanubrutinib, a BTK inhibitor, in patients with relapsed/refractory (R/R) B-cell malignancies.

Design: BGB-11417 (40, 80, 160, 320, or 640 mg once daily [QD]) with weekly or daily ramp-up to target dose was given as monotherapy or combined with zanubrutinib (320 mg QD or 160 mg twice daily) 8-12 weeks before BGB-11417. Dose-limiting toxicity was evaluated by Bayesian logistic regression. Adverse events (AEs) were reported per CTCAE v5.0.

Results: As of December 17, 2021, 58 patients received BGB-11417 (monotherapy=32; combination=26). Of patients receiving monotherapy, 26 with non-Hodgkin lymphoma (NHL; 17 diffuse large B-cell lymphoma, 6 follicular lymphoma, and 3 marginal zone lymphoma) received ≤640 mg and six with CLL/SLL received ≤160 mg; for those receiving combination

treatment, 19 with R/R CLL/SLL received BGB-11417 ≤160 mg and seven with R/R MCL received ≤80 mg. MTD has not been reached. Median follow-up was 3.9 months (range=0.1–20.4). Two grade ≥3 AEs (neutropenia=1, autoimmune hemolytic anemia=1) occurred in combination cohorts. Twenty patients discontinued treatment (disease progression=17; AE=1; other=2). One high-risk patient with CLL (monotherapy) had laboratory tumor lysis syndrome (<2%) that resolved without intervention. Early data show that most patients had a reduction in the sum of products of perpendicular diameters; two patients with NHL (monotherapy) had responses (complete response=1). Patients with CLL/SLL had notable reductions in absolute lymphocyte counts at doses ≥1 mg; two responses (≥ partial response) occurred with monotherapy and 12 with combination treatment (≥ partial response + lymphocytosis).

Conclusions: Preliminary findings suggest that BGB-11417 has promising efficacy and is tolerable at ≤640 mg as monotherapy and ≤160 mg combined with zanubrutinib. Dose escalation continues as MTD has not been reached. Enrollment is ongoing; data for Waldenström macroglobulinemia and treatment-naïve CLL/SLL are forthcoming.