Title: PHASE 1 STUDY WITH THE NOVEL BCL-2 INHIBITOR BGB-11417 AS MONOTHERAPY OR IN COMBINATION WITH ZANUBRUTINIBBRUTINIB FOR NHL OR WALDENSTRÖM MACROGLOBULINEMIA (WM): PRELIMINARY DATA

Spanish title: ESTUDIO DE FASE 1 CON EL NUEVO INHIBIDOR BCL-2 BGB-11417 COMO MONOTERAPIA O EN COMBINACIÓN CON ZANUBRUTINIBBRUTINIB PARA NHL O WALDENSTRÖM MACROGLOBULINEMIA (WM): DATOS PRELIMINARES

Authors: González Barca, E.[1]; Soumerai, J.D.[2]; Lasica, M.[3]; Opat, S.[4,5]; Cheah, C.Y.[6-8]; Chan, H.[9]; Verner, E.[10,11]; Tedeschi, A.[12]; Hilger, J.[13]; Fang, Y.[13]; Simpson, D.[13]; Tam, C.S.[5,14]

Affiliations: [1]Institut Català d'Oncologia-Hospitalet, IDIBELL, Universitat de Barcelona, Barcelona, Spain; [2]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [3]St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; [4]Monash Health, Clayton, VIC, Australia; [5]Monash University, Clayton, VIC, Australia; [6]Department of Haematology, Sir Charles Gairdner Hospital and PathWest Laboratory Medicine, Nedlands, WA, Australia; [7]Medical School, University of Western Australia, Crawley, WA, Australia; [8]Linear Clinical Research, Nedlands, WA, Australia; [9]NorthShore Hospital, Auckland, New Zealand; [10]Concord Repatriation General Hospital, Concord, NSW, Australia; [11]University of Sydney, Sydney, NSW, Australia; [12]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [13]BeiGene (Shanghai) Co., Ltd., Shanghai, China and BeiGene USA, Inc., San Mateo, CA, USA; [14]Alfred Hospital, Melbourne, VIC, Australia

ABSTRACT

Introduction: BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, phase 1/1b, dose-escalation/expansion study of BGB-11417 (a highly selective Bcl-2 inhibitor) as monotherapy or in combination with zanubrutinib, a next-generation Bruton tyrosine kinase inhibitor. Data from separate non-Hodgkin lymphoma (NHL; follicular lymphoma, diffuse large B-cell lymphoma [DLBCL], mantle cell lymphoma [MCL], marginal zone lymphoma [MZL]) and WM cohorts are presented.

Methods: Patients received BGB-11417 (40, 80, 160, 320, or 640 mg daily [QD]) with a ramp-up to the target dose. In combination cohorts, patients received zanubrutinib (320 mg QD or 160 mg twice daily) 8 to 12 weeks before BGB-11417. Dose-limiting toxicity was evaluated with a Bayesian logistic regression model. Responses were assessed per Lugano criteria.

Results: As of 15May2022, 45 patients received BGB-11417 monotherapy (≤640 mg; n=34 [28 NHL, 6 WM]) or combination treatment (tx; 11 MCL). Nine patients (82%) in combination cohorts received BGB-11417 ≤160 mg (2 patients were in zanubrutinib pre-tx). Maximum tolerated dose (MTD) was not reached in patients with NHL at doses ≤640 mg. Dose escalation is ongoing for WM monotherapy and MCL combination tx. Median follow-up was 6.5 months (range, 0.4-25.3; monotherapy) and 4.8 months (range, 0.4-8.9; combination). Tx-emergent adverse events (TEAEs) are listed in the **Table**. The most common TEAEs were nausea (38%) and fatigue (24%) for monotherapy and contusion and neutropenia (27% each) for combination tx. The most common grade ≥3 TEAEs were neutropenia (monotherapy, 12%; combination, 9%) and thrombocytopenia (combination only, 9%). Tx was discontinued in 25 monotherapy patients (disease progression [PD], n=22; AE, n=1; other, n=2) and 2 combination patients (PD). No tumor lysis syndrome was reported. 23 patients with NHL reached the first response assessment, but most were receiving below the recommended phase 2 dose (RP2D); overall, 3 responses (DLBCL, n=2; MZL, n=1), including 1 complete response (DLBCL), and notable tumor reductions were seen. In the MCL combination cohort, 6 patients (55%) responded. In the monotherapy WM cohort, 1 of 4 evaluable patients had minor response at the first dose level (80 mg), and hemoglobin increases (>20 g/L) were seen in 3 of 6 treated patients; all remain on tx.

Conclusions: Initial data show encouraging safety and antitumor activity of BGB-11417 in NHL, MCL, and WM. MTD was not reached at doses up to 640 mg QD. All low-grade TEAEs and grade ≥3 neutropenia were manageable. Longer follow-up for BGB-11417 ± zanubrutinib at the RP2D is needed. Monotherapy MCL data are forthcoming.

Table. Summary of Treatment-Emergent Adverse Events

BGB-11417 monotherapy (R/R NHL + WM; n=34)		
TEAEs (≥3 patients), n (%)	**All grade**	**Grade ≥3**
Nausea	13 (38.2)	0
Fatigue	8 (23.5)	0
Constipation	7 (20.6)	0
Diarrhea	7 (20.6)	0
Dizziness	7 (20.6)	0
Fall	6 (17.6)	2 (5.9)
Headache	6 (17.6)	0
Neutropenia (includes neutrophil count decreased)	5 (14.7)	4 (11.8)
Pyrexia	5 (14.7)	0
Abdominal pain	4 (11.8)	2 (5.9)
Anemia	4 (11.8)	1 (2.9)
Urinary tract infection	4 (11.8)	0
Vomiting	4 (11.8)	0
Arthralgia	3 (8.8)	1 (2.9)
Aspartate aminotransferase increased	3 (8.8)	1 (2.9)
Back pain	3 (8.8)	1 (2.9)
Dyspnea	3 (8.8)	0
Hypotension	3 (8.8)	0
Lethargy	3 (8.8)	0
Edema peripheral	3 (8.8)	0
Cough	3 (8.8)	0
BGB-11417 + zanubrutinibbrutinib combination (R/R MCL; n=11[a])		
TEAEs (≥2 patients), n (%)	**All grade**	**Grade ≥3**
Contusion	3 (27.3)	0
Neutropenia (includes neutrophil count decreased)	3 (27.3)	1 (9.1)
Herpes zoster	2 (18.2)	0
Lethargy	2 (18.2)	0
Nausea	2 (18.2)	0
Thrombocytopenia (includes platelet count decreased)	2 (18.2)	1 (9.1)

MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event; WM, Waldenström macroglobulinemia.

[a] Two patients had not yet received BGB-11417 at the time of analysis.