Title (Italian): STUDIO DI FASE 1 CON IL NUOVO INIBITORE B-CELL LYMPHOMA 2 (BCL-2) BGB-11417 IN MONOTERAPIA O IN COMBINAZIONE CON ZANUBRUTINIB (ZANU) IN PAZIENTI (PTS) CON LINFOMA NON-HODGKIN (NHL) O MACROGLOBULINEMIA DI WALDENSTRÖM (WM): DATI PRELIMINARI

Title (English): A PHASE 1 STUDY WITH THE NOVEL B-CELL LYMPHOMA 2 (BCL-2) INHIBITOR BGB-11417 AS MONOTHERAPY OR IN COMBINATION WITH ZANUBRUTINIB (ZANU) IN PATIENTS (PTS) WITH NON-HODGKIN LYMPHOMA (NHL) OR WALDENSTRÖM MACROGLOBULINEMIA (WM): PRELIMINARY DATA

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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 zanu, a next-generation Bruton tyrosine kinase inhibitor. Data from separate MCL, WM, and NHL (follicular lymphoma [FL], diffuse large B-cell lymphoma [DLBCL], MZL) cohorts are presented.

Methods: Pts received BGB-11417 (40, 80, 160, 320, or 640 mg QD) with a ramp-up to the target dose. In combination cohorts, pts received zanu (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 May 15, 2022, 45 pts received BGB-11417 monotherapy (≤640 mg; n=34 [28 NHL, 6 WM]) or combination treatment (tx; 11 MCL). Nine pts (82%) in combination cohorts received BGB-11417 ≤160 mg (2 pts were in zanu pre-tx). No MTD was reached in pts 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 AEs (TEAEs) across doses 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 pts (disease progression [PD], n=22; AE, n=1; other, n=2) and 2 combination pts (PD). No tumor lysis syndrome was reported. Among pts with NHL, 23 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 pts (55%) responded. In the monotherapy WM cohort, 1 of 4 evaluable pts had minor response at the first dose level (80 mg), and hemoglobin count increases of >20 g/L were seen in 3 of 6 treated pts; all remain on tx.

Conclusions: Initial data show encouraging safety and evidence of BGB-11417 efficacy 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 ± zanu 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 + zanu 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; zanu, zanubrutinib.

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