***Title (Italian)***: STUDIO DI FASE 1 CON IL NUOVO INIBITORE DI B-CELL LYMPHOMA 2 (BCL-2) BGB-11417 IN MONOTERAPIA O IN COMBINAZIONE CON ZANUBRUTINIB (ZANU) IN PAZIENTI (PTS) CON LLC/SLL: 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 CLL/SLL: PRELIMINARY DATA

**Authors**: P. Ghia[1], A. Tedeschi[2], C.Y. Cheah[3,4,5], C.S. Tam[6,7], L. Scarfò[1], M.Lasica[8], E. Verner[9,10], P.J. Browett[11], M.A. Anderson[12,13], J. Hilger[14], Y. Fang[14], D. Simpson[14], S. Opat[7,15]

**Affiliations**: [1]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele; [2]ASST Grande Ospedale Metropolitano Niguarda; [3]Department of Haematology, Sir Charles Gairdner Hospital and PathWest Laboratory Medicine; [4]Medical School, University of Western Australia; [5]Linear Clinical Research; [6]Alfred Hospital; [7]Monash University; [8]St Vincent's Hospital Melbourne; [9]Concord Repatriation General Hospital; [10]University of Sydney; [11]Department of Haematology, Auckland City Hospital; [12]Peter MacCallum Cancer Centre; [13]Division of Blood Cells and Blood Cancer, The Walter and Eliza Hall Institute; [14]BeiGene (Shanghai) Co., Ltd. and BeiGene USA, Inc.; [15]Monash Health

**Cities:** 1.2. Milan (IT), 3.5. Nedlands (AU), 4. Crawley (AU), 6.12. Melbourne (AU), 7.15. Clayton (AU), 8. Fitzroy (AU), 9. Concord (AU), 10. Sydney (AU), 11. Auckland (NZ), 13. Parkville (AU), 14. Shanghai (CN) and San Mateo (USA)

## 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 patients with CLL/SLL are presented.

**Methods:** Pts received BGB-11417 (40, 80, 160, 320, or 640 mg once daily [QD]) with a ramp-up to the intended target dose to mitigate tumor lysis syndrome (TLS). 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 during dose ramp-up through day 21. Minimal residual disease (MRD) was assessed by a European Research Initiative on CLL flow cytometry assay.

**Results:** As of May 15, 2022, 50 pts with CLL received treatment (tx): 6 had monotherapy (all relapsed/refractory [R/R]), and 44 had combination tx (R/R, n=22; tx naive [TN], n=22). The monotherapy cohort received BGB-11417 ≤160 mg, and the combination cohorts received BGB-11417 ≤640 mg (R/R CLL) or ≤320 mg (TN CLL; included 8 pts receiving zanu pre-tx and not yet treated with BGB-11417). Maximum tolerated dose had not been reached in any cohort, and dose escalation is ongoing. Median follow-up was 11.5 months (range, 8.5-18.3; monotherapy) and 5.8 months (range, 0.2-10.5; combination). Tx-emergent AEs (TEAEs) across all doses are listed in the **Table**. With monotherapy, cytopenias were the most common TEAE (≥50%; grade ≥3, 33%). With combination tx, contusion, neutropenia, and low-grade gastrointestinal toxicity were the most common TEAEs (≥23%); neutropenia was the most common grade ≥3 TEAE (11%). One pt discontinued combination tx (disease progression; Richter transformation); none discontinued monotherapy. One monotherapy pt had laboratory TLS (overall, ≤2%) that resolved without intervention. No clinical TLS was reported. Most pts had reductions in absolute lymphocyte count (ALC), with responses seen at doses of ≥1 mg. Among 4 MRD-evaluable pts at 160 mg, 3 (monotherapy, n=2; combination, n=1) had a peripheral blood CLL count of $<10^{-4}$ at 24 weeks after BGB-11417 initiation.

**Conclusions:** Preliminary data show that BGB-11417 ± zanu was well tolerated in most pts. Grade ≥3 neutropenia was uncommon and manageable, and TLS rates were low. Efficacy was supported by rapid ALC reduction during ramp-up. Enrollment for cohorts of venetoclax-treated pts with CLL/SLL will open soon.

**Table. Summary of Treatment-Emergent Adverse Events**

| **BGB-11417 monotherapy (R/R CLL; n=6)** | | |
|---|---|---|
| **TEAEs (≥2 patients), n (%)** | **All grade** | **Grade ≥3** |
| Thrombocytopenia (includes platelet count decreased) | 4 (66.7) | 2 (33.3) |
| Neutropenia (includes neutrophil count decreased) | 3 (50) | 2 (33.3) |
| Arthralgia | 2 (33.3) | 0 |
| Contusion | 2 (33.3) | 0 |
| Diarrhea | 2 (33.3) | 0 |
| Musculoskeletal chest pain | 2 (33.3) | 0 |
| Nausea | 2 (33.3) | 0 |
| Edema peripheral | 2 (33.3) | 0 |
| Pyrexia | 2 (33.3) | 1 (16.7) |
| **BGB-11417 + zanu combination (CLL; n=44)** | | |
| **TEAEs (≥3 patients), n (%)** | **All grade** | **Grade ≥3** |
| Contusion | 13 (29.5) | 0 |
| Neutropenia (includes neutrophil count decreased) | 10 (22.7) | 5 (11.4) |
| Diarrhea | 10 (22.7) | 0 |
| Nausea | 10 (22.7) | 0 |
| COVID-19 | 9 (20.5) | 1 (2.27) |
| Fatigue | 9 (20.5) | 0 |
| Headache | 8 (18.2) | 0 |
| Constipation | 7 (15.9) | 0 |
| Arthralgia | 6 (13.6) | 0 |
| Petechiae | 6 (13.6) | 0 |
| Back pain | 4 (9.1) | 0 |
| Immunization reaction | 4 (9.1) | 0 |
| Thrombocytopenia (includes platelet count decreased) | 4 (9.1) | 0 |
| Abdominal pain | 3 (6.8) | 1 (2.27) |
| Epistaxis | 3 (6.8) | 0 |
| Seasonal allergy | 3 (6.8) | 0 |

CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event; zanu, zanubrutinib.