Title: Preliminary Safety Data From Patients (pts) With Relapsed/Refractory (R/R) B-Cell Malignancies Treated With the Novel B-Cell Lymphoma 2 (BCL2) Inhibitor BGB-11417

Authors: Chan Y. Cheah, MBBS, FRACP, FRCPA, DMedSc[1,2,3]; Emma Verner, MBBS, BMedSci, FRCPA, FRACP[4,5]; Constantine S. Tam, MBBS, MD[6-9]; James Hilger, PhD[10]; Yujuan Gao, PhD[10]; Jane Huang, MD[10]; David Simpson, MBChB, FRACP, FRCPA[10]; and Stephen Opat, MBBS (Hons), FRACP, FRCPA[11,12]

Affiliations: *[1]Department of Haematology, Sir Charles Gairdner Hospital and Pathwest Laboratory Medicine, Nedlands, WA, Australia; [2]Medical School, University of Western Australia, Crawley, WA, Australia; [3]Linear Clinical Research, Nedlands, WA, Australia; [4]Concord Repatriation General Hospital, Concord, NSW, Australia; [5]University of Sydney, Sydney, NSW, Australia; [6]Peter MacCallum Cancer Centre, Melbourne, Vic, Australia; [7]University of Melbourne, Parkville, Vic, Australia; [8]St Vincent's Hospital, Fitzroy, Vic, Australia; [9]Royal Melbourne Hospital, Parkville, Vic, Australia; [10]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; [11]Monash Health, Clayton, Vic, Australia; and [12]Monash University, Clayton, Vic, Australia*

Introduction: BCL2, a key regulator of the apoptotic pathway, is aberrantly expressed in many hematologic malignancies. Treatment with BCL2 inhibitor venetoclax can be limited by common mild gastrointestinal toxicities, neutropenia, and emergence of BCL2 mutations. BGB-11417 was developed as a potent and highly selective inhibitor of BCL2 and has shown antitumor activity superior to venetoclax in acute lymphoblastic leukemia, mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL) xenograft models. BGB-11417 has a favorable pharmacokinetic profile with low plasma clearance in rodents and dogs. Toxicology study results have shown a broad safety window and excellent safety profile.

Methods: BGB-11417-101 is a first-in-human phase 1/1b study (dose escalation and safety expansion) to determine safety, tolerability, maximum tolerated dose (MTD), and recommended phase 2 dose of BGB-11417 in pts with R/R B-cell malignancies (NCT04277637). For dose escalation, pts were enrolled in 1 of 5 oral BGB-11417 dose levels (40, 80, 160, 320, or 640 mg once daily) and received weekly or daily dose ramp-up; pts with non-Hodgkin lymphomas (NHLs) received 2-day ramp-up (day 1, 25% of intended dose; day 2, 50%) before reaching the intended daily dose (day 3+, 100%). Adverse events (AEs) were reported per CTCAE v5.0. A Bayesian logistic regression model was used to evaluate dose-limiting toxicities (DLTs; during ramp-up through day 21 at intended daily dose) and determine the MTD. The first dose-

escalation cohort allowed pts with R/R follicular lymphoma (FL), marginal zone lymphoma (MZL), DLBCL, or transformed NHL.

Results: As of 01/01/2021, 7 pts with R/R NHL had been treated. A cohort of R/R chronic lymphocytic leukemia (CLL) had just opened with 2 pts treated. Only data from the NHL pts are reported (5 DLBCL, 1 FL, and 1 MZL), with median follow-up of 2.9 mo (range, 1.7-7.7). The 40-mg (n=3) and 80-mg (n=4) dose cohorts are complete with no DLTs. The 160-mg dose cohort is underway. AEs occurring in >1 pt are listed in **Table 1**. Four pts discontinued (disease progression [n=3; 2 at 40 mg, 1 at 80 mg] or lack of efficacy [n=1 at 40 mg]), and 3 pts remain on treatment. No pt discontinued from AEs, and no instances of laboratory or clinical tumor lysis syndrome were observed.

Conclusions: These early phase 1 results suggest that BGB-11417 is tolerable in pts with R/R NHL at dose levels tested. Preliminary activity in this pt population will be assessed with increased enrollment and follow-up. Enrollment of pts with R/R CLL is underway, and decreases in lymphocyte count have been seen at the initial ramp-up dose of 1 mg. Evaluation of pts with MCL and Waldenström macroglobulinemia, and the combination of BGB-11417 and Bruton tyrosine kinase inhibitor zanubrutinib, is planned for future cohorts.

Any AE in >1 Pt (N=7), n (%)	Grade ≥3	All Grade
Nausea	1 (14)	4 (57)
Constipation	0	3 (43)
AST increase	1 (14)	3 (43)
ALT increase	1 (14)	2 (29)
Dizziness	0	2 (29)
Dyspnea	0	2 (29)
Diarrhea	0	2 (29)