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

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Background: BCL2, a key protein regulator of the apoptotic pathway, is aberrantly expressed in many hematologic malignancies, which can lead to pathologic cancer cell survival. Within the cell there is a delicate balance between BH3-only proteins which activate apoptosis and BCL2 which inhibits it. BH3 mimetics have been shown to be safe and effective, resulting in their approval for the treatment of pts with chronic lymphocytic leukemia (CLL) and acute myeloid leukemia. Treatment with currently approved BCL2 inhibitor venetoclax can be limited by common mild gastrointestinal toxicities, neutropenia, and the emergence of specific BCL2 mutations around the BH3-binding groove causing resistance after continued use. BGB-11417 was developed as a potent and highly selective inhibitor of BCL2 and has shown antitumor activity superior to venetoclax in human acute lymphoblastic leukemia, mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL) xenograft models (preclinical internal data). BGB-11417 also has a favorable pharmacokinetics profile with low plasma clearance in rodents and dogs. Toxicology studies have shown a broad safety window and an excellent safety profile.

Aims: BGB-11417-101 is an ongoing first-in-human phase 1/1b study (NCT04277637) to determine the safety, tolerability, maximum tolerated dose (MTD) and recommended phase 2 dose of BGB-11417 in pts with R/R B-cell malignancies.

Methods: The study has a dose-escalation component, followed by a safety expansion. For dose escalation, pts with R/R B-cell malignancies were enrolled in 1 of 5 oral BGB-11417 dose cohorts (40, 80, 160, 320, or 640 mg once daily). All pts received a weekly or daily ramp-up to intended target dose; pts with non-Hodgkin lymphomas (NHLs) received a 2-day dose 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 Common Terminology Criteria for AEs v5.0. A Bayesian logistic regression model was used to evaluate dose-limiting toxicities (DLT; assessed during dose ramp-up through day 21 at intended daily dose) rate at different doses and to 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-Jan-2021, 7 pts with R/R NHL across 2 dose levels had been treated. The first R/R CLL cohort had just opened with 2 pts treated. Only data from the NHL pts are reported here, including: 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 have completed with no DLTs. The 160-mg dose cohort is currently being investigated. AEs across all dose levels occurring in >1 pt are listed in **Table 1**. Four pts have discontinued treatment (due to 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 due to AEs, and no instances of laboratory or clinical tumor lysis syndrome have been observed.

Conclusion/Summary: These early phase 1 results suggest that the BCL2 inhibitor 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 already been seen at the initial ramp-up dose of 1 mg. Evaluation of pts with MCL and Waldenstrom 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 (14.3)	4 (57.1)
Constipation	0	3 (42.9)
AST increase	1 (14.3)	3 (42.9)
ALT increase	1 (14.3)	2 (28.6)

Dizziness	0	2 (28.6)
Dyspnea	0	2 (28.6)
Diarrhea	0	2 (28.6)

ALT, alanine aminotransferase; AST, asparatate aminotransferase.