A PHASE 1 STUDY WITH THE NOVEL B-CELL LYMPHOMA 2 (BCL2) INHIBITOR BGB-11417 AS MONOTHERAPY OR IN COMBINATION WITH ZANUBRUTINIB (ZANU) IN PATIENTS (PTS) WITH B-CELL MALIGNANCIES: PRELIMINARY DATA

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Background: BCL2 is aberrantly expressed in many hematologic malignancies and promotes tumorigenesis by enabling cells to evade apoptosis. BCL2 inhibitors have an established role in the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and acute myeloid leukemia. The currently approved BCL2 inhibitor, venetoclax, is associated with mild gastrointestinal toxicities, neutropenia, and the development of BCL2 mutations leading to resistance. BGB-11417 is a highly selective inhibitor of BCL2 with superior potency to venetoclax in human acute lymphoblastic leukemia, mantle cell lymphoma (MCL) cell lines, and xenograft model of diffuse large B-cell lymphoma (DLBCL). BGB-11417 has favorable pharmacokinetics with excellent bioavailability and selectivity for BCL2. Toxicology studies have shown a broad therapeutic index and an improved safety profile.

Aims: BGB-11417-101 is an ongoing first-in-human phase 1/1b dose-escalation and expansion study (NCT04277637) evaluating the safety, tolerability, maximum tolerated dose (MTD), and recommended phase 2 dose of oral BGB-11417 as monotherapy or in combination with the BTK inhibitor ZANU, in pts with B-cell malignancies.

Methods: In separate monotherapy and combination therapy dose-escalation cohorts, pts with relapsed/refractory (R/R) B-cell malignancies received escalating doses of BGB-11417 (40, 80, 160, 320, or 640 mg once daily [QD]) with a weekly or daily ramp-up to intended target dose. Pts in the combination therapy cohorts received ZANU (320 mg QD or 160 mg twice daily) 8-12 weeks before BGB-11417. Dose-limiting toxicity for each dose cohort was evaluated by a Bayesian logistic regression model during dose ramp-up through day 21 at intended dose. Adverse events (AEs) were reported per Common Terminology Criteria for AEs v5.0.

Results: As of 17 Dec 2021, 58 pts received BGB-11417 (32 monotherapy; 26 combination). Of the pts receiving monotherapy, 26 with R/R non-Hodgkin lymphoma (NHL; 17 DLBCL, 6 follicular lymphoma, and 3 marginal zone lymphoma) received BGB-11417 ≤640 mg and 6 with R/R CLL/SLL received ≤160 mg. Of the pts receiving combination treatment, 19 with R/R CLL/SLL received BGB-11417 ≤160 mg and 7 with R/R MCL received ≤80 mg. MTD has not yet been reached. Median follow-up was 3.9 months (range, 0.1-20.4). AEs across all dose levels are listed in the table. Only 2 grade ≥3 AEs (1 neutropenia, 1 autoimmune hemolytic anemia) were reported in combination cohorts. Twenty pts discontinued treatment (17 disease progression; 1 AE; 2 other reasons). One high-risk pt with CLL on monotherapy had laboratory tumor lysis syndrome (TLS) that resolved with no intervention (laboratory TLS <2%). Efficacy data are early: most pts had reduction in sum of product of perpendicular diameters; 2 pts with NHL (monotherapy) achieved responses (1 complete response). Pts with CLL/SLL had notable reductions in absolute lymphocyte count at doses as low as 1 mg; 2 responses (partial response or better) were seen with monotherapy and 12 responses with combination (partial response with lymphocytosis or better).

Conclusion/Summary: These preliminary data show promising efficacy for BGB-11417 and an improved safety profile, particularly in combination cohorts. Grade ≥3 neutropenia was uncommon. BGB-11417 is tolerable up to doses of 640 mg as monotherapy and up to 160 mg in combination with ZANU. Dose escalation continues as an MTD has not yet been reached in any dose-escalation cohort. Enrollment continues, with data for Waldenström macroglobulinemia and treatment-naïve CLL/SLL cohorts forthcoming.

Table

BGB-11417 Monotherapy (n=32)		
Any AE in >10% of patients n (%)	**Grade ≥3**	**All Grade**
Nausea	0	12 (37.5)
Diarrhea	0	8 (25.0)
Fatigue	0	8 (25.0)
Neutropenia	6 (18.8)	8 (25.0)
Pyrexia	1 (3.1)	6 (18.8)
Constipation	0	5 (15.6)
Dizziness	0	5 (15.6)
Fall	2 (6.3)	5 (15.6)
Headache	0	5 (15.6)
Abdominal Pain	2 (6.3)	4 (12.5)
Oedema peripheral	0	4 (12.5)
Thrombocytopenia	2 (6.3)	4 (12.5)
Urinary tract infection	0	4 (12.5)
BGB-11417 + Zanubrutinib Combination (n=26)		
Contusion	0	6 (23.1)
Nausea	0	6 (23.1)
Diarrhea	0	5 (19.2)
Fatigue	0	4 (15.4)
Back pain	0	3 (11.5)
Headache	0	3 (11.5)
Petechiae	0	3 (11.5)