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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ABSTRACT

BCL2 is aberrantly expressed in many hematologic malignancies and promotes tumorigenesis. The BCL2 inhibitor, venetoclax, is associated with mild gastrointestinal toxicities, neutropenia, and development of BCL2 mutations leading to resistance. BGB-11417-101 (NCT04277637) is an ongoing first-in-human phase 1/1b dose-escalation and expansion study to evaluate safety, tolerability, maximum tolerated dose (MTD), and recommended phase 2 dose of oral BGB-11417 alone or combined with the BTK inhibitor zanu, in pts with relapsed/refractory (R/R) B-cell malignancies. Pts in separate monotherapy and combination therapy cohorts received escalating BGB-11417 doses (40, 80, 160, 320, or 640 mg once daily [QD]) with weekly or daily ramp-up to the target dose; combination cohorts received zanu (320 mg QD or 160 mg twice daily) 8-12 wks before BGB-11417. Dose-limiting toxicity for each dose cohort was evaluated by a Bayesian logistic regression model. Adverse events (AEs) were reported per CTCAE v5.0. As of 17Dec2021, 58 pts received BGB-11417 (32 monotherapy; 26 combination).

Of pts receiving BGB-11417 monotherapy, 26 with non-Hodgkin lymphoma (NHL) received doses ≤640 mg and 6 with CLL/SLL received ≤160 mg. Of 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 mo (range, 0.1-20.4). AEs are listed in the **table**. Only 2 grade ≥3 AEs (1 neutropenia, 1 autoimmune hemolytic anemia) were reported in combination cohorts. 20 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%). Early efficacy data show that most pts had reduction in sum of product of perpendicular diameters; 2 pts with NHL (monotherapy) had 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) were seen with monotherapy and 12 responses with combination (≥partial response with lymphocytosis). These preliminary findings suggest that BGB-11417 has promising efficacy and is tolerable at doses ≤640 mg as monotherapy and ≤160 mg in combination with zanu. Dose escalation continues as an MTD has not yet been reached. Enrollment is ongoing, data for Waldenström macroglobulinemia and treatment-naïve CLL/SLL cohorts are forthcoming.

Table. Safety Summary

BGB-11417 Monotherapy (n=32)		
Any AE in >10% of pts, 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 + zanu 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)

AE, adverse event