A phase 1 study with the novel B-cell lymphoma 2 (Bcl-2) inhibitor BGB-11417 as monotherapy or in combination with zanubrutinib in patients with NHL, or Waldenström macroglobulinemia (WM): preliminary data

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Aim: BGB-11417-101 (NCT04277637), an ongoing, first-in-human, phase 1/1b dose-escalation/expansion study, assessed BGB-11417 (a highly selective Bcl-2 inhibitor), as monotherapy or in combination with zanubrutinib, a next-generation Bruton tyrosine kinase inhibitor, in NHL (follicular lymphoma, diffuse large B-cell lymphoma [DLBCL], mantle cell lymphoma (MCL), marginal zone lymphoma [MZL]) or WM.

Method: Patients received BGB-11417 (40mg/80mg/160mg/320mg/or 640mg once daily [QD]) with dose ramp-up. In combination cohorts, patients received zanubrutinib (320mg QD or 160mg twice daily) 8-12 weeks before BGB-11417. DLTs were assessed by a Bayesian logistic regression model. Responses were assessed per Lugano criteria.

Results: By 15May2022, 45 patients received BGB-11417: monotherapy (≤640mg; NHL=28, WM=6) or combination (MCL=11; 9 received ≤160mg, 2 were in zanubrutinib pretreatment). No MTD was reached for NHL at doses ≤640mg. Dose-escalation is ongoing for WM (monotherapy) and MCL (combination). Median follow-up was 6.5 months (range, 0.4-25.3; monotherapy) and 4.8 months (range, 0.4-8.9; combination). The most common treatment-emergent AEs were nausea (38%) and fatigue (24%) for monotherapy and contusion and neutropenia (27% each) for combination. The most common grade ≥3 TEAEs were neutropenia (monotherapy=12%; combination=9%) and thrombocytopenia (combination only=9%). Treatment was discontinued by 25 (monotherapy: PD=22; AE=1; other=2) and 2 (combination: PD=2). No tumor lysis syndrome occurred. Of 23 patients with NHL with first response assessments (most below recommended phase 2 dose [RP2D]), 3 responded (DLBCL=2; MZL=1), with 1 CR. With MCL combination treatment, 6 patients (55%) responded. With WM monotherapy, 1 of 4 evaluable patients had a minor response (80mg); 3 of 6 patients had hemoglobin increases (>20 g/L), and all remain on treatment.

Conclusion: Initial data show encouraging safety and antitumor activity of BGB-11417 in NHL and WM. MTD was not reached at doses ≤640 mg QD. Low-grade TEAEs and grade ≥3 neutropenia were manageable. Longer follow-up for BGB-11417 ± zanubrutinib at the RP2D is needed.