BGB-11417 (Bcl-2 Inhibitor) Monotherapy or Combination with Zanubrutinib in Non-Hodgkin Lymphoma or Waldenström macroglobulinemia Patients

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ABSTRACT

Background

The combination of Bcl-2 and Bruton tyrosine kinase (BTK) inhibitors is tolerable with synergistic activity in chronic lymphocytic leukemia, small lymphocytic lymphoma, and mantle cell lymphoma (MCL). BGB-11417 is a novel Bcl-2 inhibitor that is more potent and selective than venetoclax. Zanubrutinib, a next-generation BTK inhibitor, has favorable activity and safety in B-cell malignancies. BGB-11417-101 is an ongoing phase 1/1b dose-escalation/expansion study (NCT04277637). Data from separate cohorts of MCL, Waldenström macroglobulinemia (WM), and combined non-Hodgkin lymphoma (NHL; follicular lymphoma [FL], diffuse large B cell lymphoma [DLBCL], marginal zone lymphoma [MZL], transformed FL) are presented.

Methods

Monotherapy: BGB-11417 40, 80, 160, 320, or 640mg QD with a ramp-up to the intended dose. Combination: zanubrutinib (320mg QD or 160mg BID) 8-12weeks before BGB-11417. Dose-limiting toxicity was evaluated during ramp-up through intended dose day 21. Responses were assessed per Lugano criteria. Adverse events (AEs) were reported per Common Terminology Criteria for AEs v5.0.

Results

As of 15 May 2022, 45 patients with NHL, WM, or MCL received BGB-11417 (34 monotherapy; 11 combination). Monotherapy: n=28 (NHL) and n=6 (WM) received BGB-11417 doses ≤640mg. Combination: n=11 (MCL) received zanubrutinib; 9 (82%) also received BGB-11417 doses ≤160mg (includes 2 patients in zanubrutinib pretreatment).

Escalation to 640mg was completed for NHL monotherapy; maximum tolerated dose (MTD) was not reached. Dose escalation is ongoing for monotherapy in WM and combination in MCL. Median follow-up: Monotherapy, 6.5months (range 0.4-25.3); Combination, 4.8months (range 0.4-8.9). Most common treatment-emergent AEs (TEAEs): Monotherapy, nausea (38%); grade ≥3, neutropenia (12%); Combination, contusion, and neutropenia (27% each); grade ≥3, neutropenia and thrombocytopenia (9% each). Treatment discontinuations: Monotherapy, n=22 disease progression (PD), n=1 AE, n=2 other reasons; Combination, n=2 PD. No TEAEs lead to death; no tumor lysis syndrome was reported. Of 23 patients who reached the first response assessment time point (most below recommended phase 2 dose [RP2D]), 3 responded (n=2 DLBCL, n=1 MZL) including 1 CR (DLBCL). MCL combination cohort, 6/11 (55%) responded. WM monotherapy cohort, 1/4 (25%) exhibited minor response at 80mg. Hemoglobin count increases >20g/L were seen in 3/6 treated patients; all remain on treatment.

Conclusion

Initial data show an encouraging safety profile and evidence of efficacy for BGB-11417 in NHL, MCL, and WM cohorts. MTD was not reached at highest dose (640mg QD). All low-grade TEAEs and grade ≥3 neutropenia were manageable. Longer follow-up of BGB-11417 monotherapy and combination therapy at the RP2D is needed. Monotherapy MCL data are forthcoming.