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 Non-Hodgkin's Lymphoma or Waldenström Macroglobulinemia: Preliminary Data

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SUMMARY

Context

The combination of a Bcl-2 inhibitor and a BTK inhibitor is well tolerated with synergistic activity in chronic lymphocytic leukemia and mantle cell lymphoma (MCL). BGB-11417 is a novel inhibitor of Bcl-2 (iBcl-2) that is more potent and selective than venetoclax. Zanubrutinib, next-generation iBTK, has favorable activity and tolerability in B-lymphoid hematological diseases. BGB-11417-101 is a Phase 1/1b study in dose escalation and expansion (NCT04277637). Data from separate cohorts of patients with MCL, Waldenström's macroglobulinemia (MW) and non-Hodgkin lymphoma (NHL; Follicular L [LF], diffuse large B-cell L [DLBCB], marginal zone L [LZM], transformed LF) are presented.

Methods

In monotherapy (MT) cohorts, patients received BGB-11417 (40, 80, 160, 320 or 640 mg 1x/d) with a gradual dose escalation to the intended dose. In combined treatment (TC) cohorts, patients received zanubrutinib (320 mg 1x/d or 160 mg 2x/d) 8-12 weeks prior to BGB-11417. Dose-limiting toxicity was assessed during the gradual dose increase up to day 21 of the predicted dose. Responses were assessed according to Lugano criteria, adverse events (AEs) were reported.

Results

As of May 15, 2022, 45 patients with NHL, MW or MCL have received BGB-11417 (34, MT; 11, TC). In the TM cohort, 28 NHL patients and 6 MW received doses of BGB-11417≤640 mg. In the TC cohort, 11 MCL patients received zanubrutinib; 9 (82%) also received doses of BGB-11417≤160 mg (including 2 pretreated with zanubrutinib). For TM NHL, the dose was gradually increased to 640 mg, the maximum tolerated dose (MTD) was not reached. Dose escalation is ongoing in MT in MW and TC in MCL. The median TM follow-up was 6.5 months (range: 0.4 to 25.3) and 4.8 months in TC (range: 0.4 to 8.9). In TM, the most common treatment-related secondary effects (TEEIs) (≥20%) were nausea (38%), fatigue (24%), constipation, diarrhea (21%) and dizziness (21%), and neutropenia (12%) for grade ≥3 ETIs. In TC, the most common ETIs were bruising (27%) and neutropenia (27%), and neutropenia and thrombocytopenia (9% each) for grade ≥3 ETEIs. 25 patients on TM (disease progression, n=22; AE, n=1; other reasons, n=2) and 2 patients on TB (progression) discontinued treatment. No EETS resulted in death and no tumour lysis syndrome was reported. Of the 23 patients who reached the first point of assessment of response (most below the recommended dose for Phase 2), 3 responded (DLBCL, n=2; LZM, n=1), including 1 complete response (DLBCL). In the MCL TC cohort, 6/11 responded. In the MW TM cohort, 1/4 had a minor response to 80 mg. Increases in haemoglobin >2 g/dl were observed in 3/6 treated patients, all of whom remain treated.

Conclusion

Initial data show an encouraging safety profile and evidence of efficacy of BGB-11417 in the NHL, LCM and MW cohorts. DMT was not achieved at the highest dose (640 mg/d). All low-grade EIETs and grade ≥ 3 neutropenia were manageable, longer follow-up of BGB-11417 in MT and TC is still required. Data on TM MCL will be available soon.