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 CLL/SLL: Preliminary Data

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SUMMARY

Context

Bcl-2 inhibitors are effective in treating CLL and lymphocytic lymphoma (LL), but the emergence of resistance limits their use. The combination of the Bcl-2 inhibitor venetoclax with Bruton tyrosine kinase (BTK) inhibitors has synergistic activity in CLL and satisfactory tolerability. BGB-11417 is a new Bcl-2 inhibitor that is more potent and selective than venetoclax. Zanubrutinib, a next-generation BTK inhibitor, has superior efficacy and a more favourable safety profile compared to ibrutinib (Brown JR, LBA-6, ASH 2022). BGB-11417-101 is a Phase 1/1b dose escalation/expansion study (NCT04277637) evaluating BGB-11417 in patients with lymphoid B hematological malignancy; data from CLL/LL cohorts are presented.

Methods

In a cohort on monotherapy (TM) and another on combination therapy (TC), patients received increasing doses of BGB-11417 (40, 80, 160, 320 or 640 mg 1x/d), with the gradual increase in doses aimed at reducing the risk of tumour lysis syndrome (SLT). TC cohorts received zanubrutinib (320 mg 1x/d or 160 mg 2x/d) from 8-12 weeks prior to BGB-11417. Dose-limiting toxicity was assessed in each cohort during dose escalation up to day 21 at the predicted dose. The adverse events (AEs) were reported according to the Common Terminology Criteria for AR v5.0. Residual disease (MRD) was assessed.

Results

As of May 15, 2022, 50 CLL patients have received treatment: 6 MTs (all relapsed/refractory [R/R]) and 44 TCs (22 R/R; 22 treatment-naïve [NT]). Doses of BGB-11417 were as follows: TM cohort up to 160 mg, R/R CLL cohort on TC up to 640 mg, CLL NT cohort on TC up to 320 mg (including 8 patients pretreated with zanubrutinib). The maximum tolerated dose has not been reached, dose escalation is ongoing. The median follow-up was 11.5 months (range: 8.5-18.3) in the TM cohort and 5.8 months (range: 0.2-10.5) in the TC cohort. The most common emerging AEs under TM treatment were cytopenias (50%), with 33% grade ≥3; under TC, these were bruises, neutropenia (11.4% grade ≥3) and low-grade gastrointestinal toxicity (22.7%). An interruption occurred in the TC cohort (disease progression, Richter transformation). Biological TLS occurred in 1 high-risk TM patient (resolved without intervention). No clinical TLS has been reported. Diarrhoea was predominantly grade 1, with no grade ≥3 cases. Early efficacy data indicate notable reductions in lymphocytosis with observed responses at 1 mg. 4 responses (66%, partial response [PR] or better) were observed with TM and 32 responses (72.7%, PR with lymphocytosis or better) with TC. MRD data are early (4 evaluable patients for MRD at 160 mg); 3 patients (2, TM; 1, TC) had peripheral blood CLL $<10^{-4}$ 24 weeks after the start of BGB-11417.

Conclusion

Based on preliminary data, BGB-11417 (in MT and TC) is well tolerated. Grade ≥3 neutropenia is uncommon and manageable. TLS levels remain low and early response data is promising, with a small subset of patients with undetectable MRD 24 weeks after treatment. Mature MRD data will soon be available and CLL/LL cohorts under venetoclax will soon be open for inclusion.