BGB-11417 (Bcl-2 Inhibitor) Monotherapy or Combination with Zanubrutinib in CLL/SLL Patients: Preliminary Phase 1 Data

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ABSTRACT

Background

Bcl-2 inhibitors are effective for treating chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL); however, the emergence of resistance limits their utility. The combination of Bcl-2 and Bruton tyrosine kinase (BTK) inhibitors is tolerable with synergistic activity in CLL. 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 CLL/SLL patients. BGB-11417-101 is an ongoing phase 1/1b dose-escalation/expansion study (NCT04277637) in patients with B-cell malignancies; data from CLL/SLL cohorts are presented.

Methods

In separate Monotherapy/Combination cohorts, patients received escalating doses of BGB-11417 (40, 80, 160, 320, or 640mg QD) with a dose ramp-up to minimize tumor lysis syndrome (TLS) risk. Combination cohorts: zanubrutinib (320mg QD or 160mg BID) beginning 8-12weeks before BGB-11417. Dose-limiting toxicity for each cohort was evaluated during ramp-up through intended-dose day 21. Adverse events (AEs) reported per Common Terminology Criteria for AEs v5.0. Minimal residual disease (MRD) was assessed by a European Research Initiative on CLL flow cytometry assay.

Results

As of 15 May 2022, 50 CLL patients received treatment: 6 monotherapy (all relapsed/refractory [R/R]) and 44 combination (22 R/R; 22 treatment naïve [TN]). BGB-11417 doses: Monotherapy, up to 160mg; combination R/R CLL, up to 640mg; TN CLL, up to 320mg (includes 8 patients in zanubrutinib pretreatment). Maximum tolerated dose has not been reached; dose escalation is ongoing. Median follow-up: Monotherapy, 11.5months (range, 8.5-18.3); Combination, 5.8months (range, 0.2-10.5). Most common treatment-emergent AEs (TEAEs): Monotherapy, thrombocytopenia and neutropenia (both ≥50%; grade≥3, 33%); Combination, contusion, neutropenia (grade ≥3, 11.4%), and low-grade gastrointestinal toxicity (all ≥22.7%). One discontinuation (Combination: disease progression; Richter transformation). Laboratory TLS (Monotherapy: 1 high-risk patient; resolved with no intervention). No clinical TLS reported. Diarrhea was mostly grade 1; none were grade≥3. Early efficacy data: notable reductions in absolute lymphocyte count (ALC); responses seen at 1mg dose. Four responses (66%), partial response [PR] or better, were observed with Monotherapy and 32 responses (72.7%), PR with lymphocytosis or better, with combination. Early MRD data (4 MRD-evaluable patients at 160mg); 3 (2 Monotherapy; 1 Combination) had a peripheral blood CLL count $<10^{-4}$ at 24 weeks after BGB-11417 initiation.

Conclusion

Preliminary data show BGB-11417 (monotherapy and combination with zanubrutinib) is well-tolerated. Grade ≥3 neutropenia was uncommon and manageable. TLS rates are low. Early MRD response data are promising; mature MRD data are forthcoming. Venetoclax-treated CLL/SLL cohorts will soon be open for enrollment.