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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ABSTRACT

Rationale: 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. CLL/SLL cohort data are presented.

Method: Patients received BGB-11417 (40mg/80mg/160mg/320mg or 640mg once daily [QD]) with dose ramp-up to mitigate tumor lysis syndrome (TLS). In combination cohorts, patients received zanubrutinib (320mg QD or 160mg twice daily) 8-12 weeks before BGB-11417. A Bayesian logistic regression model evaluated dose-limiting toxicity during dose ramp-up through day 21. Minimal residual disease (MRD) was assessed per European Research Initiative on CLL flow cytometry assay.

Results: By 15 May 2022, 50 patients with CLL received treatment: n=6 monotherapy (all relapsed/refractory [R/R]) and n=44 combination (R/R, n=22; treatment naïve [TN], n=22). The monotherapy cohort received BGB-11417 doses ≤160mg; combination cohorts received doses ≤640mg (R/R) or ≤320mg (TN; n=8 in zanubrutinib pretreatment not yet dosed with BGB-11417). With dose escalation ongoing, no cohort reached maximum tolerated dose. Median follow-up was 11.5 months (range 8.5-18.3; monotherapy) and 5.8 months (range 0.2-10.5; combination). With monotherapy, cytopenias were the most common treatment-emergent AEs (TEAEs; ≥50%; grade ≥3, 33%). With combination treatment, contusion, neutropenia, and low-grade gastrointestinal toxicity were most common (≥23%); neutropenia was the most common grade ≥3 TEAE (11%). One patient discontinued combination treatment (disease progression; Richter transformation); none discontinued monotherapy. One patient (monotherapy) had laboratory TLS (overall ≤2%) that resolved without intervention. No clinical TLS occurred. Most patients had reduced absolute lymphocyte counts with responses seen with ≥1mg. Among 4 MRD-evaluable patients (160mg), 3 (n=2

monotherapy, n=1 combination) had peripheral blood CLL counts $<10^{-4}$ at 24 weeks after BGB-11417 initiation.

Conclusion: Preliminary data show that BGB-11417 ± zanubrutinib was well tolerated. Grade ≥3 neutropenia was uncommon and manageable; TLS rates were low. Efficacy was supported by rapid ALC reduction during ramp-up.