Trial in progress: a phase II, multicenter, single-arm study of zanubrutinib (BGB-3111) in patients with previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma intolerant of prior treatment with ibrutinib.

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Background:
Ibrutinib (ibr), a Bruton tyrosine kinase inhibitor (BTKi), was shown to improve patient outcomes in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); however, adverse events (AEs) were the most common reason for discontinuing ibr (50% and 63% of discontinuations in relapse/refractory (R/R) and frontline patients, respectively; *Haematologica.* 2018:103:874). Zanubrutinib, an approved BTKi for mantle cell lymphoma, was specifically engineered to optimize selectivity. Pooled clinical data from 6 zanubrutinib monotherapy trials in B-cell malignancies (N=682 patients; R/R CLL/SLL [n=91]) suggested that zanubrutinib monotherapy was well tolerated and demonstrated a low rate of treatment discontinuation from AEs (9%; Tam, EHA 2019). Presented here is a trial-in-progress that will evaluate whether zanubrutinib monotherapy may serve as a therapeutic option for patients with CLL/SLL who have become ibr intolerant.

Methods:
The ongoing phase II, multicenter, US, single-arm, open-label study (NCT04116437, BGB-3111-215) will evaluate zanubrutinib monotherapy (160mg twice daily) as a treatment option for patients with CLL/SLL intolerant to prior ibr treatment. Approximately 60 patients will be enrolled from ~30 community medical centers. Key inclusion criteria include CLL/SLL requiring treatment per International Workshop on CLL criteria (*Blood.* 2018;131:2745) before ibr therapy, intolerance to ibr (defined as an unacceptable AE for which, per investigator's opinion, ibr treatment should be discontinued despite optimal supportive therapy), resolution of ibr-related AEs to grade ≤1 or baseline, and an ECOG PS 0-2. Key exclusion criteria include having an intervening cancer therapy between ibr and zanubrutinib, a documented disease progression during ibr treatment up to the time of enrollment, and a history of central nervous system (CNS) hemorrhage. The primary endpoint is frequency and severity of protocol-specified treatment-emergent AEs (diarrhea, myalgia, muscle spasm, arthralgia, hypertension, fatigue, rash, atrial fibrillation, and hemorrhage excluding CNS hemorrhage). The secondary endpoints include overall response rate, progression-free survival, and patient-reported outcomes. An exploratory endpoint was added to evaluate clinical effects (physical activity, treatment-related symptoms, and quality of life) using a smartphone app. Recruitment is ongoing. Clinical trial information: NCT04116437.