Zanubrutinib in Combination with Venetoclax for Patients with Treatment-Naïve (TN) Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) with del(17p): Early Results from Arm D of the SEQUOIA (BGB-3111-304) Trial

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Background: Zanubrutinib is a selective next-generation Bruton tyrosine kinase (BTK) inhibitor designed to have high specificity for BTK and minimize off-target effects (*J Med Chem* 2019;62:7923-40). Data from several phase 2 CLL trials assessing BCL-2 and BTK inhibitor combination treatment suggested that undetectable minimal residual disease (uMRD)-driven fixed-duration combination treatment was tolerable and enabled durable responses after treatment discontinuation (*JAMA Oncol* 2021;1649.; EHA 2021 S147). However, a limited number of patients with the high-risk feature, deletion of chromosome 17p13.1 [del(17p)], have been included in these studies. Preliminary data from Arm C of the SEQUOIA trial suggested that zanubrutinib monotherapy was active (18-mo progression-free survival: 90.6%) and well-tolerated in CLL/SLL patients with del(17p) (ASH 2020 1306). Here, we present early results for patients with TN del(17p) CLL/SLL receiving zanubrutinib + venetoclax in Arm D of the SEQUOIA trial (NCT03336333).

Methods: SEQUOIA is an open-label, global, multicenter, phase 3 study that includes a nonrandomized cohort (Arm D) of patients with TN del(17p) CLL/SLL (*Blood* 2020;136 [supplement 1]:24-5). Patients in Arm D were treated with zanubrutinib (160 mg twice daily) for 3 mos followed by zanubrutinib (same dosing) + venetoclax (ramp-up cycle followed by 400 mg once daily) combination treatment for 12–24 cycles until progressive disease (PD), unacceptable toxicity, or achievement of uMRD at $<10^{-4}$ sensitivity by flow cytometry (whichever occurred first). Adult patients with CLL/SLL who met International Workshop on CLL (iwCLL) criteria for treatment (*Blood* 2008;111:5446-56) were eligible if they had central verification of del(17p) by fluorescence in situ hybridization with >7% aberrant nuclei present. Initial safety and tolerability of zanubrutinib + venetoclax was assessed, including the risk of tumor lysis syndrome (TLS) both at baseline and prior to initiation of venetoclax. Responses for CLL and SLL were investigator-assessed per modified iwCLL criteria (*Blood* 2008;111:5446-56; *J Clin Oncol* 2012;30:2820-2) and Lugano criteria (*J Clin Oncol* 2014;32:3059-68), respectively. Bone marrow exams to confirm a suspected complete response (CR) or CR with incomplete hematological recovery were required starting at the end of Cycle 9.

Results: As of 1 JUN 2021 (data cutoff), 35 of approximately 80 planned patients with centrally confirmed del(17p) were enrolled. Median follow-up was 9.7 mos. In the safety analysis population (n=35), 94.3% had CLL and high-risk characteristics including Binet stage C (51.5%), bulky disease ≥5 cm

(42.9%), unmutated immunoglobulin heavy chain variable locus (85.3%, n=34), median del(17p) frequency of 81.5%, and elevated β_2-microglobulin (71.4%). At data cutoff, 29 patients had started combination therapy and 27 patients completed ramp-up venetoclax dosing. Thirty-two patients remained on study treatment and 3 patients ended treatment due to withdrawal of consent, PD, or adverse event (AE of lung cancer), all n=1. The patient with lung cancer had lung nodules present at screening and died due to lung adenocarcinoma. AEs and serious AEs were reported in 29 patients (82.9%) and 4 patients (11.4%), respectively. AEs reported in ≥10% of patients included diarrhea (n=5), neutropenia (n=5), fatigue (n=4), nausea (n=4), and petechiae (n=4). Thirteen patients (37.1%) had grade ≥3 AEs; most frequently neutropenia (n=4) and diarrhea (n=2). One patient with ongoing grade 2 atrial fibrillation at baseline reported grade 3 atrial fibrillation on study. To date, no AEs of TLS have been reported. At baseline, the TLS risk categories were high, medium, and low in 12 (34.3%), 22 (62.9%), and 1 (2.9%) patients, compared with 0 (0%), 21 (67.7%), and 10 (32.3%) patients, respectively, prior to initiation of venetoclax. For the 31 patients who reached the initial efficacy assessment at 3 mos after starting zanubrutinib, the overall response rate was 96.8% (30/31); one patient reported PD after having an initial partial response while on combination therapy.

Conclusion: Preliminary safety data with the 9.7-mo median follow-up suggest that zanubrutinib + venetoclax was generally well tolerated in this high-risk population, with no new safety signals identified and no TLS reported. Enrollment is ongoing; updated safety, efficacy, and biomarker data will be presented.

Table: Preliminary Summary of Safety and Efficacy

Safety	
	TN del(17p) CLL/SLL (n = 35)
Median follow-up, mo (range)	9.72 (4.53–16.36)
Any AE, n (%)	29 (82.9)
Grade ≥3 AE, n (%)	13 (37.1)
Serious AE, n (%)	4 (11.4)
Treatment discontinuation due to AE, n (%)	1 (2.9)
Fatal AE, n (%)	1 (2.9)
Efficacy (Best Response)	
	TN del(17p) CLL/SLL (n = 31)
Median follow-up, mo (range)	11.2 (3.0–18.5)
ORR (CR/CRi, PR, or PR-L), n (%) [95% CI]	30 (96.8) [69.7–95.2]
CR/CRi	4 (12.9)
PR	22 (71.0)
PR-L	4 (12.9)
SD	1 (3.2)
PD	0 (0)

AE, adverse event; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete hematological recovery; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, PR with lymphocytosis; SD, stable disease; SLL, small lymphocytic lymphoma; TN, treatment-naïve.