Efficacy and Safety of Zanubrutinib in Patients with Treatment-Naive Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) with Del(17p): Initial Results from Arm C of the Sequoia (BGB-3111-304) Trial

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Background: Patients with CLL/SLL whose tumor exhibits the deletion of chromosome 17p13.1 [del(17p)] have an unfavorable prognosis and respond poorly to standard chemoimmunotherapy. Several new options targeting B-cell receptor signaling have emerged as potential effective therapies in this high-risk group. Zanubrutinib (BGB-3111) is an investigational, next-generation Bruton tyrosine kinase (BTK) inhibitor, designed to

maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases. It has been shown to be highly potent, selective, and bioavailable with potentially advantageous pharmacokinetic and pharmacodynamic properties. In an early phase study, zanubrutinib demonstrated complete and sustained BTK occupancy in both peripheral blood mononuclear cells and lymph nodes and has been associated with durable clinical responses in patients with CLL/SLL (Tam, *Blood* 2019). Here, we present safety and efficacy data in treatment-naive (TN) patients with del(17p) CLL/SLL who are enrolled in the non-randomized Arm C of the SEQUOIA (BGB-3111-304) trial.

***Methods**:* The SEQUOIA trial is an open-label, global, multicenter, phase 3 study that includes a non-randomized cohort (Arm C) of TN patients with del(17p) CLL/SLL treated with zanubrutinib (160 mg twice daily). Adult patients with CLL/SLL who met iwCLL criteria for treatment (Hallek, *Blood* 2008) were eligible if they were either ≥ 65 y of age or unsuitable for treatment with fludarabine, cyclophosphamide, and rituximab. Use of long-term anticoagulation was permitted. Central verification of del(17p) by fluorescence in situ hybridization with a minimum of 7% aberrant nuclei present was required for entry into Arm C. Response assessment was evaluated by investigator for CLL per modified iwCLL criteria (Hallek, *Blood* 2008; Cheson, *J Clin Oncol* 2012) and for SLL per Lugano criteria (Cheson, *J Clin Oncol* 2014).

***Results**:* In total, 109 patients with centrally confirmed del(17p) were enrolled into Arm C (complete accrual). As of 19 April 2019 (data cutoff), all patients had received ≥1 dose of zanubrutinib and were included in the safety analysis. Median age was 70.0 y (range, 42-86) and median follow-up in the safety analysis set was 6.3 mo (Table 1). At data cutoff, 106 patients remained on study treatment. Adverse events (AEs) reported in ≥10% of treated patients included contusion (20.2%), rash (11.0%), upper respiratory tract infection (10.1%), and nausea (10.1%). Grade ≥3 AEs were reported in 33 patients (30.3%). Grade ≥3 AEs that occurred in >1 patient included neutropenia/decreased neutrophil count (n = 10), anemia, pneumonia, nephrolithiasis, and hypertension (each n = 2). One patient died due to grade 5 pneumonia that occurred 8 days after the last dose of zanubrutinib. AEs of interest (pooled terms) included infections (39.4%), bruising (24.8%), minor bleeding (18.3%), neutropenia (13.8%), arthralgia/myalgia (8.3%), diarrhea (8.3%), anemia (6.4%), hypertension (6.4%), thrombocytopenia (5.5%), fatigue (5.5%), headache (4.6%), petechiae (4.6%), second

primary malignancy (2.8%), and major bleeding (2.8%). To date, no AEs of atrial fibrillation have been reported. At data cutoff, 90 patients were evaluable for efficacy with median follow-up of 7.0 mo; of these, 87 patients remained on study treatment. The overall response rate was 92.2% (Table 2). Two patients had disease progression due to Richter transformation and 1 patient died due to grade 5 pneumonia. No patient had progressed with CLL/SLL.

Conclusions*:* In this study, we have completed enrollment of one of the largest prospective cohorts of TN patients with del(17p) CLL/SLL. Preliminary results suggested that zanubrutinib was active and generally well tolerated. Clinical trial information: NCT03336333.

Table 1: Key Patient Characteristics and Safety

	TN del(17p) CLL/SLL (n = 109)
Median follow-up, mo (range)	6.31 (1.9-14.5)
Demographics	
Median age, y (range)	70.0 (42-86)
Male sex, n (%)	78 (71.6)
ECOG PS 2, n (%)	14 (12.8)
Disease Characteristics	
SLL, n (%)	11 (10.1)
Binet stage C, n (%)	40 (40.8)
del(13q), n (%)	72 (66.1)
del(11q), n (%)	37 (33.9)
Trisomy 12, n (%)	20 (18.3)
IGHV mutational status Mutated, n (%) Unmutated, n (%) QNS[a], n (%)	 36 (33.0) 67 (61.5) 6 (5.5)
Bulky disease[b], n (%) Any TL LDi ≥ 5 cm Any TL LDi ≥ 10 cm	 46 (42.2) 18 (16.5)
Safety	
Any AE, n (%)	93 (85.3)
Grade ≥3 AE, n (%)	33 (30.3)
Serious AE, n (%)	19 (17.1)
Treatment discontinuation due to AE, n (%)	1 (0.9)
Fatal AE, n (%)	1 (0.9)

AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; QNS, quantity not sufficient; TL, target lesion; LDi, longest diameter

[a]RNA quantity/quality not sufficient for PCR amplification of VH region for sequencing.

[b]Patients with any target lesion with longest diameter presented.

Table 2: Summary of Efficacy (Best Response)

	TN del(17p) CLL/SLL (n = 90)[a]
Median follow-up, mo (range)	7.0 (2.9-14.5)
Efficacy (best response)	
ORR (CR, PR, or PR-L), n (%) [95% CI][b]	83 (92.2) [84.6-96.8]
CR	0 (0.0)
PR	68 (75.6)
PR-L	15 (16.7)
SD	6 (6.7)
PD	1 (1.1)

CR, complete response; ORR, overall response rate; PD, progressive disease, PR, partial response, PR-L, PR with lymphocytosis; SD, stable disease.

[a]Subset of patients who had ≥1 response assessment as of 19 April 2019; no patients discontinued prior to first response assessment.

[b]2-sided Clopper-Pearson 95% confidence intervals.