**Title: Efficacy and Safety of Zanubrutinib in Patients with Treatment-Naïve (TN) Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) with del(17p): Follow-up Results from Arm C of the SEQUOIA (BGB-3111-304) Trial**

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***Background:*** Patients (pts) with CLL/SLL whose tumor exhibits the deletion of chromosome 17p13.1 [del(17p)] have an unfavorable prognosis and respond poorly to standard chemoimmunotherapy. Zanubrutinib (BGB-3111) is an investigational, next-generation Bruton tyrosine kinase (BTK) inhibitor. In the ASPEN study of pts with Waldenström macroglobulinemia, zanubrutinib was associated with important safety advantages compared to ibrutinib, especially regarding cardiovascular toxicity (*Blood;* in press). The initial results from Arm C of the SEQUOIA (BGB-3111-304) trial of zanubrutinib in a large cohort of TN CLL/SLL pts with del(17p) were recently presented with a median follow-up of 10 months (*Blood* 2019;134:851). Presented here is an updated analysis for safety and efficacy in this cohort.

***Methods****:* The SEQUOIA trial (NCT03336333) is an open-label, global, multicenter, phase 3 study that includes a nonrandomized cohort (Arm C) of TN pts with del(17p) CLL/SLL treated with zanubrutinib (160 mg twice daily). Adult pts with CLL/SLL who met International Workshop on CLL (iwCLL) criteria for treatment (*Blood* 2008;111:5446) were eligible if they were aged ≥65 y 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 was evaluated by investigator for CLL per modified iwCLL criteria (*Blood* 2008;112:5259; *J Clin Oncol.* 2012;30:2820) and for SLL per Lugano criteria (*J Clin Oncol.* 2014;32:3059).

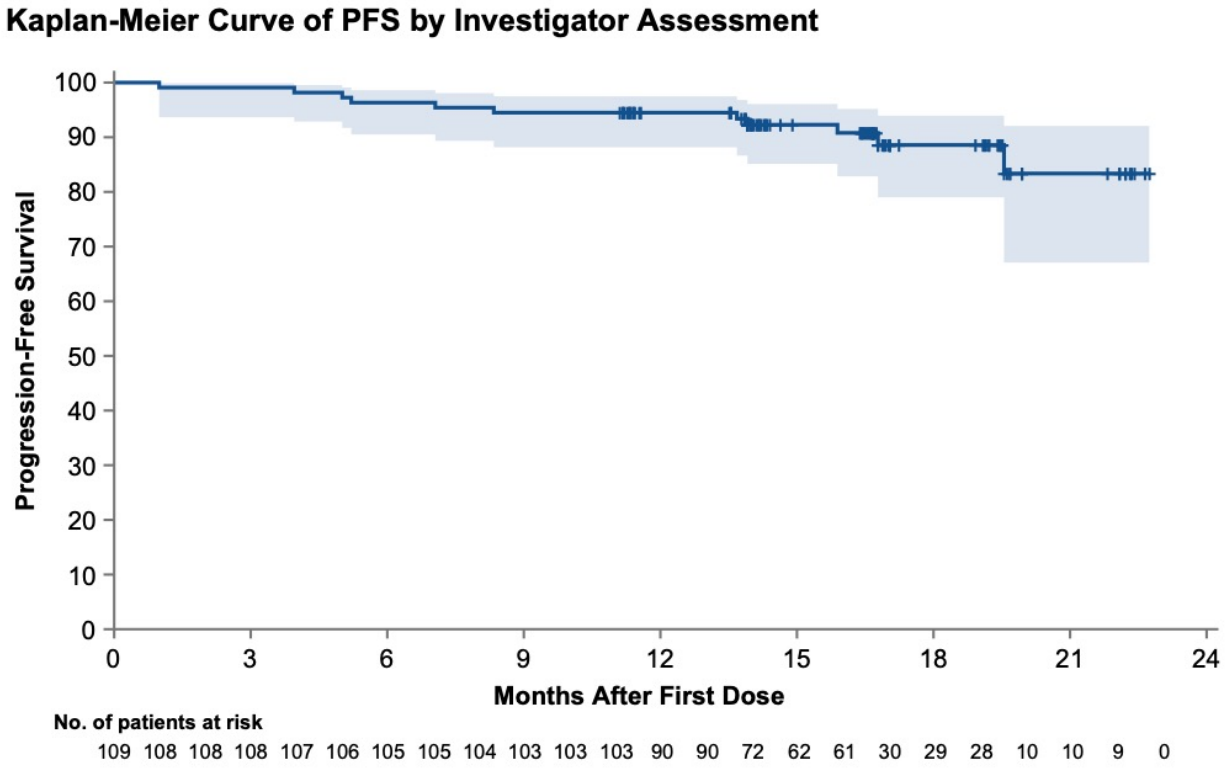
***Results****:* As of 15 Apr 2020 (data cutoff), median follow-up was 18.2 mo (range, 5.0-26.3) for the 109 pts enrolled; 97 pts (89.0%) remained on treatment with zanubrutinib. The best overall response rate (ORR) was 94.5% (3.7% complete response [CR] or CR with incomplete bone marrow recovery, 87.2% partial response [PR], 3.7% PR with lymphocytosis, 4.6% stable disease, 0.9% progressive disease). Five pts (4.6%) met clinical CR criteria but did not undergo bone marrow biopsy. Median progression-free survival (PFS), duration of response (DoR), and overall survival (OS) were not reached. Estimated 18-mo PFS (**Figure)**, 18-mo DoR, and 18-mo OS were 88.6% (95% CI, 79.0-94.0), 84.0% (95% CI, 67.5-92.6), and 95.1% (95% CI, 88.4-97.9), respectively. Investigator-reported transformation occurred in 5 pts (4.6%), of whom 4 had histologic confirmation. Median time to transformation was 13.6 mo (time to transformation for each pt: 3.9, 7.0, 13.6, 13.8, and 15.7 mo). In an exploratory analysis, 37.2% and 26.7% of pts with evaluable karyotypes had at least 3 or 5 distinct karyotypic abnormalities, respectively; no differences in ORR or PFS were observed between pts with or without complex karyotype.

With extended follow-up, adverse events (AEs) reported in ≥10% of treated pts included contusion (20.2%), upper respiratory tract infection (19.3%), neutropenia/neutrophil count decreased (17.4%), diarrhea (16.5%), nausea (14.7%), constipation (13.8%), rash (13.8%), back pain (12.8%), cough (11.9%), arthralgia (11.0%), and fatigue (10.1%). Grade ≥3 AEs occurring in >2% of pts included neutropenia/neutrophil count decreased (12.9%) and pneumonia (3.7%). AEs of interest (pooled terms) included infections (64.2%), bleeding (47.7%; 5.5% grade ≥3 or serious), headache (8.3%), hypertension (8.3%), and myalgia (4.6%). Skin tumors were reported in 9.2%, and non-skin second malignancies were reported in 4.6% of pts. Three pts (2.8%) reported an AE of atrial fibrillation or flutter of which 2 events occurred in the setting of sepsis. Four pts (3.7%) discontinued zanubrutinib due to AEs (including pneumonia, sepsis secondary

to *Pseudomonas*, melanoma, and acute kidney injury [in the context of disease progression]), of which 2 pts have died. Three additional pts died, 2 due to disease progression and 1 from sepsis after progression. No sudden or unknown deaths were reported.

***Conclusions****:* Extended follow-up of zanubrutinib monotherapy in TN CLL/SLL pts with del(17p) showed the durability of responses in this high-risk cohort, with an estimated 18-mo PFS of 88.6% and estimated 18-mo OS of 95.1%. Zanubrutinib was generally well tolerated, with low rates of discontinuation due to AEs. These data support the potential utility of zanubrutinib in the frontline management of pts with high-risk disease.

**Figure**




CI, confidence interval; PFS, progression-free survival.
Shaded area indicates 95% CI.