**Title: Zanubrutinib in Combination with Venetoclax for Patients with Treatment-Naïve Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma and del(17p): Arm D of the SEQUOIA (BGB-3111-304) Trial**

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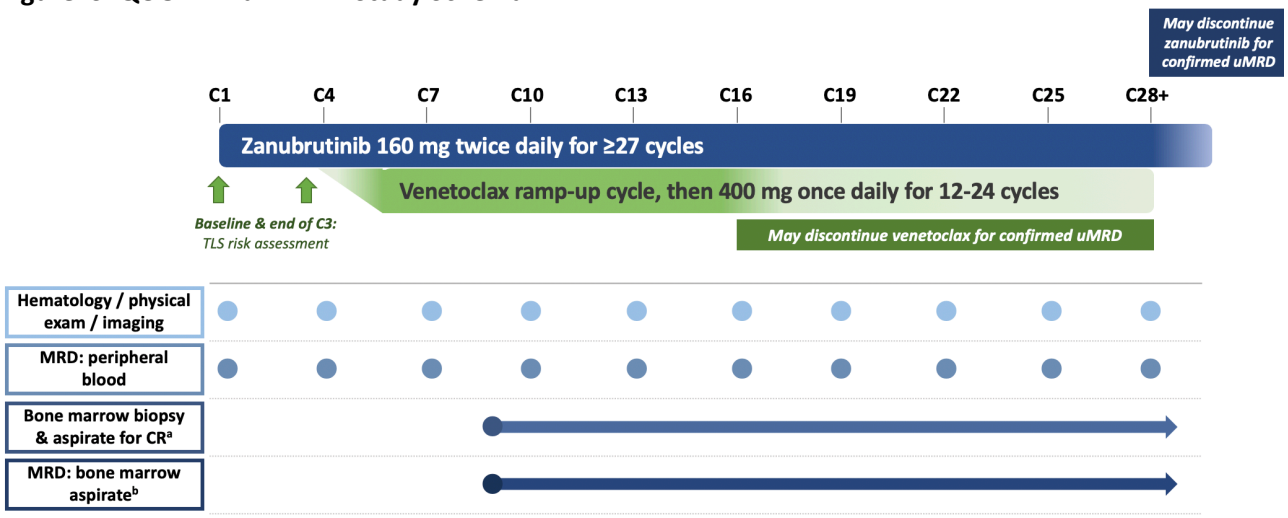
***Background:*** Zanubrutinib is a highly selective, next-generation Bruton tyrosine kinase (BTK) inhibitor designed to maximize BTK occupancy and minimize off-target effects. Zanubrutinib has been associated with improved specificity and durable clinical responses in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; Tam, *Blood* 2019;134:851-9). Early clinical data from Arm C of the SEQUOIA trial suggested that zanubrutinib was active and well-tolerated in treatment-naïve (TN) CLL/SLL patients with the high-risk characteristic deletion of chromosome 17p13.1 [del(17p)] (Tam ASH 2019 #499). In that cohort, an overall response rate (ORR) of 92.7% was reported, and the most common adverse events (AEs; 20.1% contusion, 15.6% upper respiratory tract infection, 13.8% rash) and most common grade ≥3 AEs (10.1% neutropenia, 3.7% pneumonia, 2.8% hypertension) were consistent with those in previous reports of zanubrutinib treatment in patients with various B-cell malignancies.

Venetoclax is a B-cell lymphoma 2 protein (BCL-2) inhibitor approved for the treatment of adult patients with CLL or SLL. Results of several phase 2 CLL trials of BCL-2 inhibitor and BTK inhibitor combinations have suggested that combination treatment is tolerable and may have synergistic activity (Hillmen *JCO* 2019;37:2722-9. Jain, *NEJM* 2019;380:2095-103. Siddiqi, EHA 2020 #S158.). Combination treatment given for a finite duration as determined by undetectable minimal residual disease (uMRD) is of significant interest and has the potential to alter the CLL/SLL treatment landscape if shown to induce deeper responses with a fixed duration of therapy. In the BOVen study, zanubrutinib was given in combination with venetoclax and obinutuzumab to TN CLL patients, and uMRD in the peripheral blood and bone marrow was used to determine treatment discontinuation (Soumerai, ASCO 2020 #8006.) Preliminary data showed that 62% of patients met the uMRD endpoint and successfully discontinued treatment after a median of 8 months (6 months of triplet therapy), and 100% of patients had a best response of partial response or higher (43% complete response/complete response with incomplete marrow recovery). The most common grade ≥3 AEs (15.4% neutropenia, 5.1% thrombocytopenia, 5.1%

lung infection, 2.6% infusion-related reaction, 2.6% rash, 2.6% bleeding) were consistent with those previously reported in combination treatment studies, and no events of tumor lysis syndrome (TLS) were reported.

***Study Design and Methods**:* The SEQUOIA trial (NCT03336333) is an open-label, global, multicenter, phase 3 study that includes a nonrandomized cohort (Arm D) of up to 50 TN patients with del(17p) CLL/SLL. Arm D is designed to provide combination treatment of zanubrutinib and venetoclax and use serial monitoring of uMRD to determine treatment discontinuation. Patients are treated with zanubrutinib (160 mg twice daily) for 3 months followed by the combination of zanubrutinib (same dosing) and venetoclax (ramp-up cycle followed by 400 mg once daily). Combination treatment is given for 12-24 cycles until disease progression, unacceptable toxicity, or requirements for uMRD at $<10^{-4}$ sensitivity (uMRD4) by flow cytometry are met (Figure). Adult patients with CLL/SLL who met International Workshop on CLL (iwCLL) criteria for treatment (Hallek, *Blood* 2008;111:5446-56) are eligible if they have central verification of del(17p) by fluorescence in situ hybridization with >7% aberrant nuclei present. Initial safety and tolerability of zanubrutinib and venetoclax combination therapy will be assessed, including the risk of TLS at baseline and before initiation of venetoclax. Responses will be assessed by investigator for CLL per modified iwCLL criteria (Hallek, *Blood* 2008;111:5446-56. Cheson, *JCO* 2012;30:2820-2) and for SLL per Lugano criteria (Cheson, *JCO* 2014;32:3059-68). Secondary endpoints include ORR, progression-free survival, duration of response, rate of uMRD4 at various time points, safety, and pharmacokinetics of zanubrutinib and venetoclax. Exploratory endpoints include overall survival, patient-reported outcomes, and time to recurrence of detectable MRD after discontinuation of zanubrutinib and/or venetoclax. Recruitment began in November 2019 and is ongoing in 8 countries.

**Figure: SEQUOIA Trial Arm D Study Schema**




C, cycle; CR, complete response; CRi, CR with incomplete blood count recovery; PD, progressive disease; TLS, tumor lysis syndrome; uMRD, undetectable minimal residual disease (at $<10^{-4}$ sensitivity by flow cytometry).
[a]Bone marrow biopsy and aspirate are required to confirm a suspected CR/CRi, starting after cycle 9 and then annually if needed.
[b]Patients with confirmed CR/CRi and two negative peripheral blood MRD tests must have two consecutive bone marrow aspirate MRD tests that meet uMRD requirements for dose stopping.