Zanubrutinib vs bendamustine + rituximab (BR) in patients with treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma: extended follow-up of the SEQUOIA study

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Introduction:

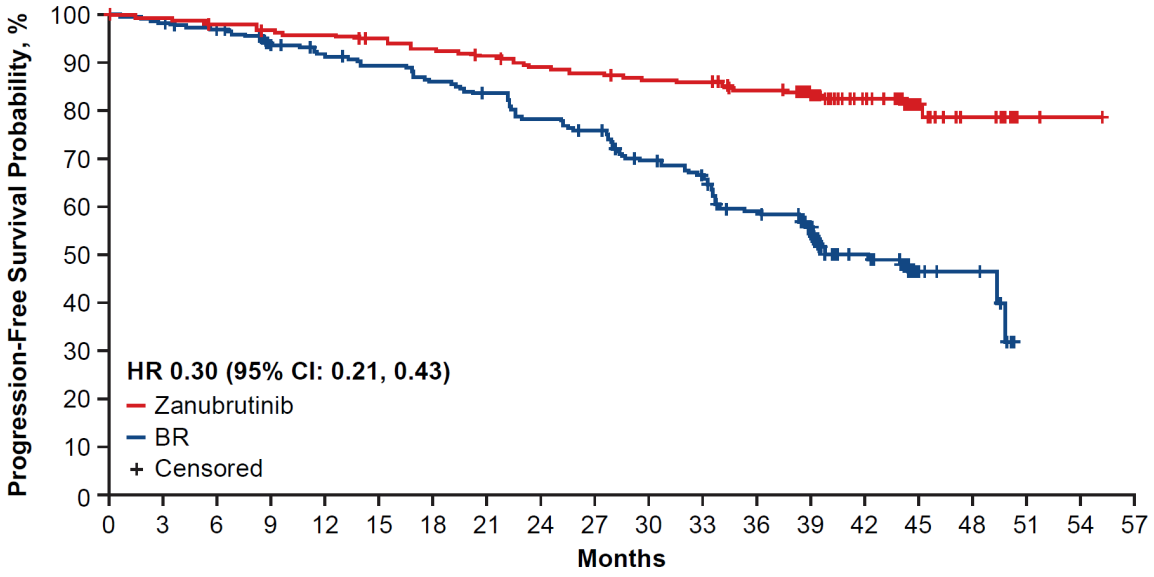
Zanubrutinib is a next-generation Bruton tyrosine kinase (BTK) inhibitor designed to minimize off-target binding and limit associated side effects that is approved in the US and EU for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Results from the SEQUOIA study (NCT03336333), at a median follow-up of 26.2 months, demonstrated superior progression-free survival (PFS) by independent review for zanubrutinib vs BR in patients with treatment-naive CLL/SLL without del(17p); patients with del(17p) treated with zanubrutinib in a separate cohort had similar outcomes to patients without del(17p). We report updated efficacy and safety results from the SEQUOIA study after approximately 18 months of additional follow-up.

Methods:
Patients without del(17p) were randomized to receive zanubrutinib or BR. Patients with del(17p) were assigned to zanubrutinib monotherapy. Investigator-assessed (INV) PFS, overall survival (OS), overall response rate (ORR), and safety/tolerability were evaluated. Adverse events (AEs) were recorded until disease progression or start of next-line therapy.

Results:
As of 31 October 2022, a total of 479 patients without del(17p) were randomized to receive zanubrutinib (n=241) or BR (n=238). At a median follow-up of 43.7 months (range, 0-60 months), median PFS was not reached with zanubrutinib; however, median PFS with BR was 42.2 months (HR, 0.30; 95% CI, 0.21-0.43; **Figure**). At 42 months, the estimated PFS rate was 82.4% with zanubrutinib. With additional follow-up, PFS with zanubrutinib vs BR was improved for patients with mutated *IGHV* (HR, 0.35; 95% CI, 0.19-0.64) and was sustained in patients with unmutated *IGHV* (HR, 0.23; 95% CI, 0.14-0.37) or del(11q) (HR, 0.26; 95% CI, 0.13-0.51). Complete response/complete response with incomplete hematologic recovery (CR/CRi) rates in patients without del(17p) were 17.4% and 21.8% with zanubrutinib and BR, respectively. While median OS was not reached in either arm, the HR for OS was 0.87 (95% CI, 0.50-1.48) with zanubrutinib vs BR and the estimated 42-month OS rates were 89.4% and 88.3%, respectively. For 110 patients with del(17p) assigned to zanubrutinib monotherapy, after a median follow-up of 47.9 months, the estimated 42-month PFS and OS rates were 79.4% and 89.5%, respectively. In this population, the CR/CRi rate was 14.5%. As of 31 Oct 2022, zanubrutinib treatment was ongoing in 74.7% patients without del(17p) and 70.3% patients with del(17p). The most common causes for treatment discontinuation were AEs and progressive disease for both patients without del(17p) (14.9%, 5.8%, respectively) and with del(17p) (13.5%, 13.5%). AEs of interest (AEI), using pooled terms, were as expected for the class in patients without del(17p) (zanubrutinib vs BR). AEI included any-grade atrial fibrillation/flutter (5.0% vs 2.6%), hypertension (17.5% vs 13.7%), bleeding (48.8% vs 12.3%), infection (72.9% vs 62.6%), anemia (7.1% vs 20.7%), thrombocytopenia (6.3% vs 18.1%), and neutropenia (16.7% vs 56.8%). Additionally, grade ≥3 AEI included bleeding (5.8% vs 1.8%), infection (23.8% vs 22.0%), anemia (0.4% vs 2.2%), thrombocytopenia (2.1% vs 7.9%), and neutropenia (12.5% vs 51.1%).

Conclusions:
Extended follow-up SEQUOIA data demonstrated that the efficacy of zanubrutinib was maintained in patients without del(17p) with a safety profile aligned with long-term follow-up for the BTK inhibitor class. Longer follow-up showed benefit in patients with mutated *IGHV*. Patients with del(17p) continue to demonstrate PFS benefits consistent with the randomized cohort. Zanubrutinib continues to be well tolerated with low rates of treatment discontinuation and remains a valuable frontline treatment option for CLL/SLL.

Figure: Progression-Free Survival by Investigator Assessment



No. of Patients at Risk																			
Zanubrutinib	241	238	234	230	228	224	219	214	208	205	201	200	190	131	93	33	23	4	3	0
BR	238	218	212	201	192	187	180	174	163	157	141	133	113	82	50	18	8	0		