Sustained superiority of zanubrutinib vs bendamustine + rituximab in treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (TN CLL): 5-year follow-up of cohort 1 from the SEQUOIA study

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Introduction: SEQUOIA (NCT03336333) is a multicenter, open-label, randomized phase 3 study evaluating the safety and efficacy of the next-generation Bruton tyrosine kinase (BTK) inhibitor zanubrutinib (zanu) in TN CLL/SLL. Cohort 1 enrolled patients without del(17p) to zanu or bendamustine + rituximab (BR). At a median follow-up of 26.2 months, the primary analysis demonstrated that zanu had a superior progression-free survival (PFS) compared with BR. Presented here are long-term data with 5 years of overall study follow-up for cohort 1.

Methods: As previously reported, patients without del(17p) were randomized to zanu (160 mg twice daily until progressive disease or unacceptable toxicity) or BR. Patients in the BR arm were permitted to cross over to zanu monotherapy after disease progression. Adverse events (AEs) were reported until disease progression or start of next-line therapy. This follow-up analysis evaluated efficacy and safety, including investigator-assessed PFS, overall survival (OS), and overall response rate (ORR). PFS and OS analyses were also adjusted for COVID-19 impact. *P* values were descriptive.

Results: A total of 479 patients were randomized to receive zanu (n=241) or BR (n=238). Arms were well balanced for demographic and disease characteristics; the median patient age was 70 years, 52% had unmutated IGHV, and 14% had a complex karyotype with ≥3 abnormalities. As of April 30, 2024, the median follow-up was 61.2 months (range, 0.0-74.7) and median zanu exposure was 60.5 months (range, 0.5-77.9). Of patients in the BR arm, 25% (n=59) crossed over to receive zanu monotherapy. Median PFS was not reached for zanu and was 44.1 months (95% CI, 38.4-55.6) for BR (hazard ratio [HR], 0.29; 95% CI, 0.21-0.40; 1-sided *P*<.0001). Estimated 54-month PFS rates were 80% (95% CI, 74-85%) for zanu and 45% (95% CI 38-51%) for BR, and estimated 60-month PFS rates were 76% (95% CI, 69-81%) for zanu and 40% (95% CI, 33-47%) for BR. With adjustment for COVID-19 impact, estimated 54-month PFS rates were 83% (95% CI, 78-88%) for zanu and 45% (95% CI 38-52%) for BR, and estimated 60-month PFS rates were 79% (95% CI, 72-84%) for zanu and 41% (95% CI, 33-48%) for BR. PFS benefit was sustained for zanubrutinib regardless of IGHV mutation status (vs BR, mutated IGHV (HR, 0.40; 95% CI, 0.23-0.69; 1-sided *P*=.0003) and unmutated IGHV (HR, 0.21; 95% CI, 0.14-0.33; 1-sided *P*<.0001). Median OS was not reached in either treatment arm; estimated 54-month OS rates were 88% (95% CI, 83-91%) for zanu and 86% (95% CI, 81-90%) for BR, and 60-month OS rates were 86% (95% CI, 81%-90%) for zanu and 85% (95% CI, 80%-89%) for BR. With adjustment for COVID-19 impact, estimated 54-month OS rates were 91% (95% CI, 87-94%) for zanu and 88% (95% CI, 83-92%) for BR, and estimated 60-month OS rates were 89% (95% CI, 84-93%%) for zanu and 87% (95% CI, 81-91%) for BR. ORR was 98% with zanu and 89% with BR, including CR/CRi rates of 21% with zanu and 24% with BR. All-grade (gr) and gr ≥3 adverse events (AEs) occurred in 95% and 68% of patients in the zanu arm, respectively, and 97% and 83% of the BR arm. Serious AEs occurred in 57% (zanu) and 83% (BR). AEs of interest for the zanu vs BR arms included atrial fibrillation (AF)/flutter (any gr, 7% vs 4%; gr ≥3, 1% vs 2%), bleeding (any gr, 52% vs 13%; gr ≥3, 7% vs 2%), hypertension (any gr, 23% vs 14%; gr ≥3, 14% vs 7%), infections (any gr, 80% vs 66%; gr ≥3, 30% vs 22%), anemia (any gr, 10% vs 21%; gr ≥3, 1% vs 3%), thrombocytopenia (any gr, 7% vs 19%; gr ≥3, 2% vs 8%), and neutropenia (any gr, 17% vs 57%; gr ≥3, 12% vs 51%). Exposure-adjusted

incidence rates for select AEs of interest (person per 100 person-months; zanu vs BR) were AF/flutter (0.13 vs 0.09), hemorrhage (1.66 vs 0.35), major hemorrhage (0.18 vs 0.05), and hypertension (0.50 vs 0.38). AEs leading to death occurred in 10% (zanu) and 9% (BR) of patients, most commonly due to infections (5% and 4%, respectively). Treatment was ongoing for 68% of patients in the zanu arm.

Conclusions: Patients with TN CLL without del(17p) treated with zanu had sustained PFS vs BR in this 5-year follow-up of SEQUOIA. The PFS benefit for zanu was sustained regardless of IGHV mutation status, and CR rates continue to improve. The safety and tolerability profile of zanu was consistent with prior reports; no new safety signals were observed, and rates of AF/flutter and treatment discontinuations remained low. These long-term data continue to support the use of zanu as a standard frontline treatment for CLL/SLL.