Combination of zanubrutinib + venetoclax for treatment-naive (TN) CLL/SLL with del(17p) and/or *TP53*: preliminary results from SEQUOIA arm D

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Background: Zanubrutinib (zanu) is a next-generation, selective BTK inhibitor designed to have high BTK specificity and minimize off-target effects. In several recent studies, fixed-duration BCL2/BTK inhibitor combination treatment was tolerable and led to durable responses in patients with CLL/SLL. As monotherapies, zanu and venetoclax (ven), the first-generation BCL2 inhibitor, have achieved high ORRs in patients with del(17p) and/or *TP53* mutation.

Aims: Here, preliminary results in patients with del(17p) and/or *TP53* mutation who received zanu + ven combination treatment in the SEQUOIA trial (arm D) are presented.

Methods: SEQUOIA (NCT03336333) is an open-label, global, phase 3 study; arm D is a nonrandomized cohort of patients aged ≥65 years old (or 18-64 years old comorbidities) who had TN CLL/SLL with del(17p) and/or *TP53* mutation and met iwCLL criteria for treatment. Patients received zanu (160 mg twice daily) lead-in for 3 cycles, then zanu + ven (ramp-up to 400 mg once daily) for 24 cycles, followed by zanu monotherapy until progressive disease,

unacceptable toxicity, or meeting early dose-stopping rules for either zanu or ven (simultaneous achievement of CR/CR with incomplete hematopoietic recovery [CRi] and undetectable minimal residual disease [uMRD; $<1\times10^{-4}$ by flow cytometry in peripheral blood (PB) and bone marrow (BM) on 2 consecutive tests ≥12 weeks apart]). Responses were investigator assessed per modified iwCLL and Lugano criteria (SLL) with PB MRD assessments every 3 cycles for 2 years and then every 6 cycles. Safety per CTCAE and risk of tumor lysis syndrome (TLS) per Cairo Bishop criteria pre-treatment and prior to ven administration, were also assessed. Patients at high risk for TLS were those with any lymph node ≥10 cm or ≥5 cm with absolute lymphocyte count $\geq25\times10^{9}$/L.

Results: Between Nov 2019 and Jun 2022, 66 patients with centrally assessed del(17p) and/or *TP53* mutation were enrolled. Three discontinued treatment during the zanu lead-in period. As of Oct 31, 2023, with a median study follow-up of 28.6 months (range 0.4-47.4), 55 of 63 (87%) patients who initiated zanu + ven remained on treatment (16 on zanu + ven; 39 on zanu monotherapy after completing ven treatment). Among 66 treated patients, 52% were male and the median age was 66 years (range, 26-87). Six patients discontinued the study (4 deaths; 1 withdrawal; 1 lost to follow-up). In 65 response-evaluable patients, the ORR was 100% and the CR+CRi rate was 45% (Table). uMRD was achieved by 48% of patients in ≥1 PB sample. Median PFS was not reached and the 36-month estimated PFS was 92% (95% CI, 81%-97%). Ninety-seven percent of patients experienced ≥1 TEAE. The most common all-grade non-hematologic TEAEs were COVID-19 (55%), diarrhea (41%), contusion (29%), and nausea (29%). Grade ≥3 non-hematologic TEAEs occurred in 44% of patients; the most common were diarrhea (8%) and hypertension (8%). The most common all grade and grade ≥3 hematologic toxicity was neutropenia (21% and 17%, respectively). The proportion of patients at high risk for TLS decreased from 35% at screening to 3% after 3 cycles of lead-in zanu and no TLS was reported.

Summary/Conclusion: Preliminary data demonstrate promising efficacy and tolerability of zanu + ven combination treatment in patients with high-risk TN CLL/SLL with del(17p) and/or *TP53* mutation. The safety profile of zanu + ven was consistent with results of prior zanu studies, and no new safety signals were identified.

Table. Efficacy Outcomes in Patients With del(17p) and/or *TP53* Mutation

	del(17p)+ or *TP53*+ (n=66)
Response evaluable, n (%)[a]	65 (98)
Best overall response, n (%)	
CR+CRi	29 (45)
Nodular PR	0
PR	35 (54)
PR with lymphocytosis	1 (2)
SD	0
ORR, n (%)	65 (100)
Best uMRD rate at any time in PB, n (%)	32 (48)

[a] Patients who received ≥1 dose of zanu with ≥1 post-baseline disease assessment.