Combination of zanubrutinib (zanu) + venetoclax (ven) in patients with treatment-naive (TN) CLL/SLL with del(17p) and/or TP53: Preliminary results from SEQUOIA arm D

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ABSTRACT

Background: Combination BCL2/BTKi treatment (tx) has been tolerable and led to durable responses in patients (pts) with CLL/SLL. Here, initial results are presented in pts with TN CLL/SLL with del(17p) and/or *TP53* mutation who received zanu+ven in SEQUOIA arm D.

Methods: SEQUOIA (NCT03336333) is an open-label, global, phase 3 study; arm D includes nonrandomized pts aged ≥65 y (or 18-64 y with comorbidities) who met iwCLL 2008 criteria for tx. After a 3-cycle zanu 160 mg BID lead-in, pts had 24 cycles of zanu+ven (ramp-up to 400 mg QD), then zanu monotherapy until PD, unacceptable toxicity, or early dose-stopping rules for zanu or ven were met (simultaneous 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 wk apart). Responses were investigator assessed per modified iwCLL and Lugano 2014 criteria (SLL), with PB MRD assessment every 3 cycles for 2 y, then every 6 cycles. Safety per CTCAE and tumor lysis syndrome (TLS) risk per Cairo-Bishop criteria were also assessed. Pts with high TLS risk had any lymph node ≥10 cm or ≥5 cm with absolute lymphocyte count $\geq25\times10^{9}$/L.

Results: From Nov 2019-Jun 2022, 66 pts with centrally assessed del(17p) and/or *TP53* mutation were enrolled. By Oct 31, 2023 (median follow-up, 28.6 mo; range, 0.4-47.4), 55/63 pts (87%) who initiated zanu+ven remained on tx (16 zanu+ven; 39 zanu monotherapy after ven). Six pts discontinued the study (4 deaths; 1 withdrawal; 1 loss to follow-up); 3 discontinued tx during zanu lead-in. In 65 response-evaluable pts, ORR was 100% and CR+CRi rate was 45% (Table). uMRD occurred in 48% of pts in ≥1 PB sample. Median PFS was not reached; 36-mo estimated PFS was 92% (95% CI, 81%-97%). The most common all-grade nonhematologic TEAEs were COVID-19 (55%), diarrhea (41%), contusion (29%), and nausea (29%). Grade ≥3 nonhematologic TEAEs occurred in 44%; the most common were diarrhea (8%) and hypertension (8%). Neutropenia was the most common all-grade (21%) and grade ≥3 (17%) hematologic toxicity. At screening, 35% of pts had high TLS risk; this decreased to 3% after 3 zanu lead-in cycles. No TLS occurred.

Conclusions: Preliminary data show promising efficacy and good tolerability of zanu+ven in pts with high-risk TN CLL/SLL with del(17p) and/or *TP53* mutation. The safety profile of zanu+ven was consistent with prior studies, with no new safety signals 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)

CRi, complete response with incomplete hematopoietic recovery; uMRD, undetectable minimal residual disease.

[a] Patients who received ≥1 dose of zanu with ≥1 postbaseline disease assessment.