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

Authors: Alessandra Tedeschi,[1] Shuo Ma,[2] Talha Munir,[3] Masa Lasica,[4] Mazyar Shadman,[5,6] Emmanuelle Ferrant,[7] Ian W. Flinn,[8] Wojciech Janowski,[9] Monica Tani,[10] Tadeusz Robak,[11] Jennifer R. Brown,[12] Constantine S. Tam,[13] Tian Tian,[14] Emily Mantovani,[14] Stephanie Agresti,[14] Linlin Xu,[14] Aileen Cohen,[14] Wojciech Jurczak,[15] Paolo Ghia[16,17]

Affiliations: [1]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [2]Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [3]Leeds Teaching Hospitals NHS Trust, Leeds, UK; [4]St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; [5]Fred Hutchinson Cancer Center, Seattle, WA, USA; [6]University of Washington, Seattle, WA, USA; [7]CHU de Lyon-Sud, Lyon-Sud, France; [8]Tennessee Oncology/OneOncology, Nashville, TN, USA; [9]Calvary Mater Newcastle Hospital, Waratah, NSW, Australia; [10]Santa Maria delle Croci Hospital, Ravena, Italy; [11]Copernicus Memorial Hospital, Medical University of Łódź, Łódź, Poland; [12]Dana-Farber Cancer Institute, Boston, MA, USA; [13]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [14]BeiGene USA, Inc, San Mateo, CA, USA; [15]Maria Sklodowska-Curie National Research Institute of Oncology, Kraków, Poland; [16]Università Vita-Salute San Raffaele, Milano, Italy; [17]IRCCS Ospedale San Raffaele, Milano, Italy

ABSTRACT

Introduction: Combination BCL2/BTK inhibitor 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 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%. 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.

Conclusion: 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.