Evaluation of factors from established prognostic models in patients with chronic lymphocytic leukemia (CLL) treated with zanubrutinib: a post-hoc analysis of two phase 3 studies (SEQUOIA and ALPINE)

Authors: Jessica Li,[1] Yang Shi,[2] Linlin Xu,[1] Xiaopeng Ma,[2] Marcus Lefebure,[3] Tommi Salmi,[4] Teiko Sumiyoshi,[1] Inhye E. Ahn[5]

Affiliations: [1]BeOne Medicines Ltd, San Carlos, CA, USA; [2]BeOne Medicines Ltd, Beijing, China; [3]BeOne Medicines Ltd, London, UK; [4]BeOne Medicines International GmbH, Basel, Switzerland; [5]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Background: The CLL-International Prognostic Index (IPI) is a weighted scoring system that combines 5 factors (age, clinical stage, unmutated immunoglobulin heavy chain variable region [U-IGHV], elevated beta-2 microglobulin [B2M], and *TP53* aberrations [*TP53*ab, defined as *TP53* mutations and/or del(17p)]). The CLL-IPI predicted overall survival (OS) in patients treated with chemoimmunotherapy (Hallek et al. *Lancet Oncol*. 2016) and progression-free survival (PFS) in patients primarily treated with venetoclax-based targeted therapy (Langerbeins et al. *Blood*. 2024). The 4-factor model (CLL4) was developed using data from patients receiving the BTK inhibitor (BTKi) ibrutinib and identified risk groups with distinct PFS and OS based on 4 variables (*TP53*ab, relapsed/refractory [R/R] disease, elevated B2M, and elevated lactate dehydrogenase [LDH]; Ahn et al. *J Clin Oncol*. 2021). To characterize the clinical impact of prognostic factors included in the CLL-IPI and the CLL4, as well as complex karyotype, in the context of zanubrutinib therapy, we analyzed data from the SEQUOIA and the ALPINE studies.

Methods: SEQUOIA (NCT03336333) is a phase 3 study comparing zanubrutinib (Arm A) versus bendamustine and rituximab (Arm B) in patients with treatment naïve (TN) CLL without del(17p), and, in a separate cohort, investigating zanubrutinib monotherapy in patients with del(17p) (Arm C). ALPINE (NCT03734016) is a phase 3 trial comparing zanubrutinib to ibrutinib in R/R CLL. *TP53* mutations, fluorescence in situ hybridization (FISH), IGHV, and cytogenetic status were assessed following the European Research Initiative on CLL guidelines. Specifically, we utilized centralized testing of baseline *TP53* mutations by next-generation sequencing at a Clinical Laboratory Improvement Amendments (CLIA)-certified lab (Predicine, CA, USA; reporting threshold: variant allele frequency [VAF] ≥1%) and Vysis CLL FISH for del(17p) (reporting threshold: abnormality >7%). Complex karyotype, defined as ≥3 abnormalities (CKT3), was assessed according to the International System for Human Cytogenomic Nomenclature criteria. We conducted univariable and multivariable Cox regression analyses of baseline factors among patients treated with zanubrutinib monotherapy.

Results: In this retrospective biomarker analysis, patients treated with zanubrutinib from SEQUOIA (Arms A and C, n=350) and ALPINE (zanubrutinib arm, n=327) were included. Univariable analyses demonstrated that the following variables were associated with shorter PFS in both TN and R/R CLL: elevated B2M (≥5 mg/L), elevated LDH (>250 U/L), elevated Eastern Cooperative Oncology Group performance status (≥1), and bulky disease (≥5 cm) (all *P*<.05). CKT3 and U-IGHV were associated with shorter PFS in R/R but not TN CLL. *TP53*ab was not associated with shorter PFS in TN or R/R CLL.

In multivariable analyses, of the factors found to be associated with shorter PFS in univariable analyses in TN and/or R/R CLL patients, only LDH was an independent prognostic marker for shorter PFS in TN CLL (*P*<.05). Notably, *TP53*ab did not independently predict PFS.

Conclusion: In patients with TN and R/R CLL treated with zanubrutinib in the SEQUOIA and ALPINE studies, LDH was the sole independent prognostic marker associated with PFS, and its predictive value is for patients with TN CLL only. *TP53*ab was not associated with inferior PFS in TN or R/R CLL in this post-hoc analysis. New risk-stratification tools may be warranted in the context of zanubrutinib therapy in CLL.