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)

5681

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]

[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

CONCLUSIONS

- The CLL-IPI and CLL4 models had limited value in risk stratification of patients treated with zanubrutinib. Inferior PFS was observed among the highest risk groups of these models
- In a multivariable analysis of the evaluated factors, only elevated LDH was associated with inferior PFS in patients with CLL receiving zanubrutinib as 1L therapy
- *TP53* aberrations, defined as *TP53* mutations and/or del(17p), were not independently associated with inferior PFS in the ITT populations of the SEQUOIA (TN CLL) or ALPINE (R/R CLL) trials in patients receiving zanubrutinib, suggesting the efficacy of zanubrutinib in the *TP53*ab subgroup

INTRODUCTION

- The established chronic lymphocytic leukemia (CLL) models evaluated in this study:

CLL International Prognostic Index (CLL-IPI)[1]

Purpose/setting:
- Pre-treatment risk stratification; developed in the chemoimmunotherapy era

Variables (points):
- Age >65 years (1)
- Clinical stage: Binet B/C or Rai I-IV (1)
- Serum β-2 microglobulin (B2M) >3.5 mg/L (2)
- Unmutated immunoglobulin heavy chain variable region (U-IGHV) (2)
- *TP53* aberration (*TP53*ab), defined as *TP53* mutation and/or del(17p) (4)

Score and risk group:
- 0-1 = Low risk
- 2-3 = Intermediate risk
- 4-6 = High risk
- 7-10 = Very high risk

Application:
- Widely validated; prognostic for overall survival (OS) and time to first treatment (TTFT)

CLL Four-Factor Model for Ibrutinib (CLL4)[2]

Purpose/setting:
- Risk stratification before initiation of ibrutinib

Variables (points):
- *TP53*ab (1)
- Prior treatment (relapsed/refractory) (R/R) (1)
- Serum B2M ≥5 mg/L (1)
- Lactate dehydrogenase (LDH) >250 U/L (1)

Score and risk group:
- 0-1 = Low risk
- 2 = Intermediate risk
- 3-4 = High risk

Application:
- Simple, treatment-specific model
- Validated in independent cohorts; tailored for ibrutinib context

- In this post-hoc analysis, we examined data from patients treated with zanubrutinib in the SEQUOIA (NCT03336333)[3] and ALPINE (NCT03734016)[4] trials to evaluate the CLL-IPI and CLL4 models. We assessed the clinical relevance of the individual factors included in the models, as well as bulky disease, Eastern Cooperative Oncology Group performance status (ECOG PS), and complex karyotyping

METHODS

Data Source and Analyzed Populations

- Baseline characteristics of patients included in this analysis are shown in **Table 1**
- Data from the intent-to-treat (ITT) populations receiving zanubrutinib in the SEQUOIA trial (treatment-naïve [TN] CLL; Arm A [without del(17p)] and Arm C [with del(17p)]) and the ALPINE trial (R/R CLL; Arm A) were used in these analyses
- Model parameters were assessed as previously described[5] (baseline *TP53* mutations: next-generation sequencing [NGS] at a Clinical Laboratory Improvement Amendments-certified lab [Predicine, CA, USA]; del(17p) mutations: Vysis CLL fluorescence in situ hybridization [FISH] Probe [Abbott Molecular, USA]; IGHV mutational status: Sanger sequencing and NGS IGHV assay [SEQUOIA] and a NGS IGHV assay [ALPINE]; cytogenetic analysis: stimulated culture using traditional G-banding for metaphase analysis [NeoGenomics, USA]; complex karyotype (CKT3): assessed using the International System for Human Cytogenomic Nomenclature)

Statistical Analysis

- We conducted traditional univariable and multivariable Cox regression analyses of baseline factors among patients treated with zanubrutinib monotherapy

Table 1. Baseline Characteristics of Patients Included in This Analysis

	SEQUOIA (Arm A + Arm C), n=349	ALPINE (Arm A), n=327
Median follow-up, months	62.72	43.43
Age		
Median, years (range)	70 (40-87)	67 (35-90)
≥65 years, n (%)	291 (83.4)	201 (61.5)
B2M		
Median (range), mg/L	4 (0.5-38.0)	4.3 (0.0-18.8)
≥5 mg/L, n (%)	109 (31.2)	107 (32.7)
Missing, n (%)	17 (4.9)	46 (14.1)
LDH		
Median (range), U/L	213.5 (97.0-643.0)	224 (108.0-1828.0)
>250 U/L, n (%)	98 (28.1)	118 (36.1)
Missing, n (%)	3 (0.9)	0
ECOG PS, n (%)		
≥1	197 (56.4)	198 (60.6)
Bulky disease, n (%)		
≥5 cm	111 (31.8)	145 (44.3)
Missing	11 (3.2)	0
IGHV, n (%)		
Unmutated	188 (53.9)	239 (73.1)
Missing	14 (4.0)	9 (2.8)
CKT3, n (%)[a]		
≥3	55 (15.8)	56 (17.1)
Missing	98 (28.1)	118 (36.1)
***TP53*ab, n (%)[b]**		
Yes	125 (35.8)	111 (33.9)
Missing	16 (4.6)	16 (4.9)

[a]A complex karyotype was defined as three or more abnormalities. [b]*TP53*ab were defined as *TP53* mutations and/or del(17p).

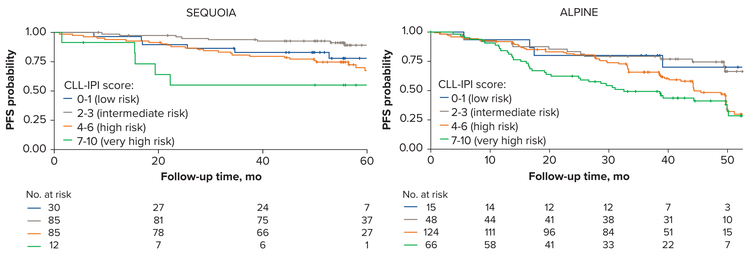
RESULTS

CLL-IPI and CLL4 Model Stratification

- The CLL-IPI and CLL4 models have limitations in stratifying patients treated with zanubrutinib in SEQUOIA and ALPINE into previously described[1,2] risk groups
- Instead, these models stratify patients into two groups, which may limit their utility for accurate treatment-related risk stratification (**Figure 1**)

Figure 1A. The CLL-IPI Model Delineates Only the "Very High Risk" Group in SEQUOIA and ALPINE

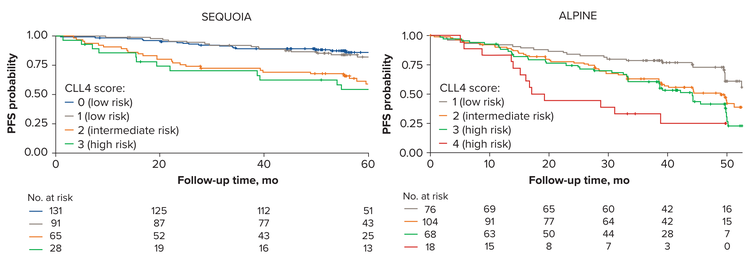
Binet stage A or B versus Binet C was used for the clinical stage classification



mo, months; PFS, progression-free survival.

Figure 1B. The CLL4 Model Cannot Delineate Patients With Scores 2 and 3

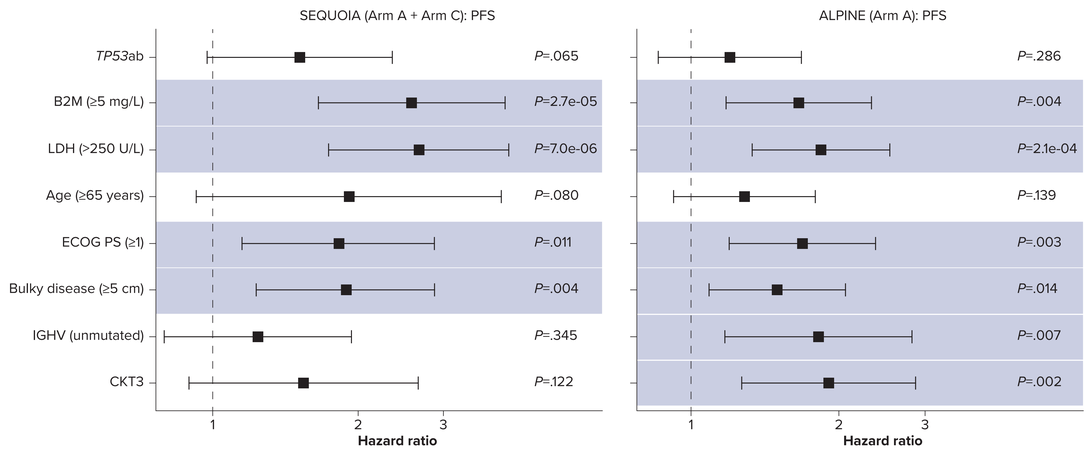
As expected, the SEQUOIA population does not have patients with a score 4, and the ALPINE population does not have patients with a score 0



Univariable PFS Cox Regression Analysis

- A univariable PFS Cox regression analysis including all evaluated variables is shown in **Figure 2**
  - *TP53*ab were not associated with inferior PFS in TN or R/R CLL
  - Elevated B2M (≥5 mg/L), elevated LDH (>250 U/L), elevated ECOG PS (≥1), and bulky disease (≥5 cm) were associated with inferior PFS in both TN and R/R CLL (all *P*<.05)
  - CKT3 and U-IGHV were associated with inferior PFS in R/R but not TN CLL (*P*<.05)

Figure 2. Forest Plot of Univariable PFS Cox Regression Analysis



Multivariable Cox Regression Analysis

- In multivariable analysis of the evaluated factors, only elevated LDH was associated with inferior PFS in patients with CLL receiving zanubrutinib as first-line (1L) therapy (**Table 2**)
- *TP53*ab were not independently associated with inferior PFS

Table 2. Multivariable Cox Regression

	SEQUOIA			ALPINE		
Factors	**HR**	**SE**	***P*-value**	**HR**	**SE**	***P*-value**
*TP53*ab	0.90	0.31	.73	1.24	0.24	.36
B2M ≥5 mg/L	1.58	0.30	.13	1.21	0.24	.44
LDH >250 U/L	**2.14**	**0.30**	**.01**	1.56	0.24	.07
Age ≥65 years	2.81	0.53	.05	0.97	0.27	.92
ECOG PS ≥1	1.59	0.31	.14	1.52	0.26	.11
Bulky disease ≥5 cm	1.77	0.31	.06	1.27	0.24	.32
U-IGHV	0.86	0.30	.62	1.45	0.35	.30
CKT3	1.39	0.34	.33	1.38	0.24	.19

Only patients with data for all analyzed variables were included in the multivariable analysis (SEQUOIA: n=205 (Arm A: n=136; Arm C, n=69); ALPINE: n=165). HR, hazard ratio; SE, standard error.

LIMITATIONS

- Our analyses have limitations, including the nature of the trial-collected data and the modest cohort sizes resulting from the availability of certain biomarker data
- Further evaluations and additional statistical analyses are needed to refine risk stratification in patients with CLL treated with zanubrutinib

REFERENCES

1. Hallek M, et al. *Lancet Oncol*. 2016;17:779-790.
2. Ahn I, et al. *J Clin Oncol*. 2021;39:576-585.
3. Tam C, et al. *Lancet Oncol*. 2022;238:1031-1043.
4. Brown JR, et al. *New Engl J Med*. 2023;388:319-332.
5. Tam C, et al. *Blood Adv*. 2025;9:2863-2870.

ACKNOWLEDGMENTS

We would like to thank the investigators, site support staff, and especially the patients for participating in this study. We would also like to thank Nicole Li, Ruiqi Huang, Jiazheng Zhang and Charles Cao for their contributions to this work. Inhye E. Ahn is a Scholar in Clinical Research supported by Blood Cancer United. This study was sponsored by BeOne Medicines Ltd. Editorial support was provided by Amiculum, and supported by BeOne Medicines Ltd.

CORRESPONDENCE: Inhye E. Ahn, inhye_ahn@dfci.harvard.edu

Presented at the 67th Annual Meeting and Exposition of the American Society of Hematology; December 6-9, 2025; Orlando, FL, USA