Long-Term Follow-Up for Safety and Efficacy of Zanubrutinib in Elderly (≥80 Years) Treatment-Naïve CLL/SLL Patients, Including Those With del(17p): Subgroup Analysis From the SEQUOIA Trial

PS1703

Alessandra Tedeschi,[1] Anders Osterborg,[2] Talha Munir,[3] Marcus Lefebure,[4] Jiayi Shen,[5] Wassim Aldairy,[5] Jamie Hirata,[5] Constantine S Tam[6]

[1]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [2]Karolinska University Hospital, Stockholm, Sweden; [3]Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; [4]BeOne Medicines, Ltd, London, United Kingdom; [5]BeOne Medicines, Ltd, San Carlos, CA, USA; [6]Alfred Health and Monash University, Melbourne, Victoria, Australia

CONCLUSIONS

- SEQUOIA includes one of the largest uniformly treated populations of treatment-naïve CLL/SLL patients aged ≥80 years, with the longest follow-up reported to date in this subgroup
- In this population, which was enriched for high-risk genomic features such as del(17p) and/or *TP53* mutations, zanubrutinib demonstrated durable clinical benefit, with high PFS rates at 72 months
- The tolerability profile observed in this subgroup was consistent with expectations for a very elderly population and aligned with the established safety profile of zanubrutinib. Rates of discontinuation due to AEs were low during the first 3 years of treatment
- Atrial fibrillation/flutter events occurred infrequently and were consistent with the general population for age-adjusted atrial fibrillation risk[1]
- These findings support zanubrutinib as an effective treatment option for treatment-naïve CLL/SLL across age groups, including very elderly patients

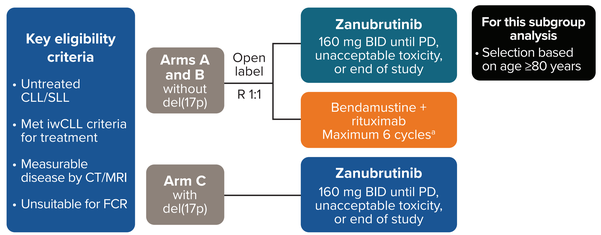
INTRODUCTION

- Chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL) predominantly affect older adults, with a median age at diagnosis of approximately 72 years. Very elderly patients (≥80 years) remain underrepresented in clinical trials, resulting in limited long-term data to inform treatment decisions in this population
- In an aging population, the incidence of adverse events (AEs) is expected to increase and accumulate with longer follow-up. For example, the risk of atrial fibrillation rises substantially with age in the general population[2]
- In the phase 3 SEQUOIA trial, the next-generation Bruton tyrosine kinase inhibitor (BTKi) zanubrutinib demonstrated superior progression-free survival (PFS) versus bendamustine plus rituximab in treatment-naïve (TN) CLL/SLL patients without del(17p), with robust efficacy also observed in patients with del(17p)[3]
- However, long-term efficacy and safety outcomes specifically in very elderly patients have not been well characterized. This subgroup analysis evaluates long-term outcomes of zanubrutinib in TN CLL/SLL patients aged ≥80 years enrolled in SEQUOIA

METHODS

- SEQUOIA is a global, randomized, open-label phase 3 study (NCT03336333) enrolling TN patients with CLL/SLL considered unsuitable for fludarabine + cyclophosphamide + rituximab[4]
- Study design is shown in **Figure 1**

Figure 1. Study Design and Subgroup Selection



[a]Bendamustine 90 mg/m² IV on days 1 and 2 for 6 cycles + rituximab 375 mg/m² IV the day before or on day 1 of cycle 1 and 500 mg/m² on day 1 of cycles 2-6.

BID, twice daily; CLL/SLL, chronic lymphocytic leukemia and small lymphocytic lymphoma; CT/MRI, computed tomography / magnetic resonance imaging; FCR, fludarabine, cyclophosphamide, and rituximab; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; PD, progressive disease; R 1:1, randomized 1-to-1.

RESULTS

Disposition and Baseline and Disease Characteristics

- Median follow-up time was 78.75 months
- A total of 38 patients aged ≥80 years treated with zanubrutinib were included in this subgroup analysis (Arm A: 28; Arm C: 10). Median age was 81 years (range, 80–87), and 60.5% of patients were male (**Table 1**)
  - Fourteen patients (36.8%) remained on treatment

Table 1. Baseline Characteristics and Disease History

	Zanubrutinib-treated patients aged ≥80 years (n=38)
Age, median (range), years	81 (80–87)
Sex, n (%)	
Male	23 (60.5)
Del(17p) and/or *TP53*mut, n (%)	
Abnormal	14 (36.8)
IGHV Status, n (%)	
Mutated	14 (36.8)
Unmutated	22 (57.9)
Unknown	2 (5.3)
Complex Karyotype, n (%)	
≥3 Copy Number Aberrations	4 (10.5)
Missing	14 (36.8)

IGHV, immunoglobulin heavy chain variable; mut, mutation.

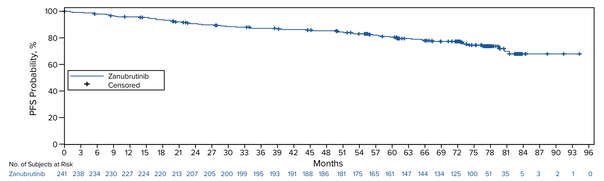
Efficacy

ITT (Intent-to-Treat)

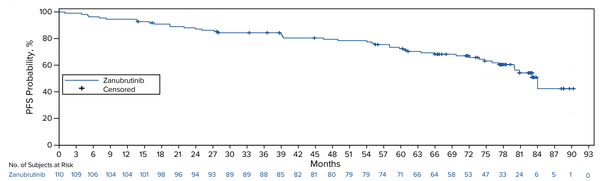
- Median follow-up for Arm A ITT (n=241) and Arm C ITT (n=111) was 79.15 months (95% confidence interval [CI]; 0.3-96.0) and 82.73 months (95% CI; 5.0-92.9), respectively
- Arm A ITT PFS estimate at 72 months was 74.4% (95% CI; 68.1, 79.6). After COVID-19 adjustment, the 72-month PFS rate was 77.3% (95% CI; 71.1, 82.3) (**Figure 2A**)
- Arm C ITT PFS estimate at 72 months was 66.3% (95% CI; 56.2, 74.5). After COVID-19 adjustment, the 72-month PFS rate was 67.0% (95% CI; 57.0, 75.3) (**Figure 2B**)
- The overall response rate (complete response / complete response with incomplete marrow recovery) was 97.5% (27.0%) and 97.3% (21.8%) in the Arm A and Arm C ITT, respectively

Figure 2. Investigator-Assessed PFS Adjusted on COVID-19 in Arm A and Arm C ITT

A. Arm A



B. Arm C

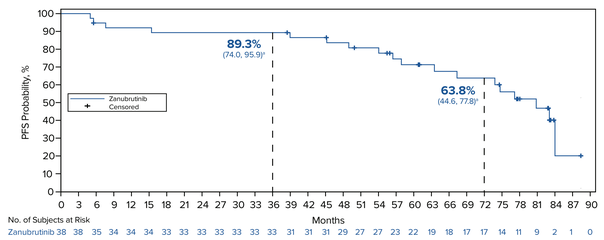


CI, confidence interval; ITT, intent-to-treat; PFS, progression-free survival.

≥80 Years Subgroup

- Investigator-assessed PFS estimate at 36 months and 72 months was 89.3% (95% CI; 74.0, 95.9) and 63.8% (95% CI; 44.6, 77.8), respectively (**Figure 3**)
- The investigator-assessed overall response rate was 100%, with a complete response rate of 18.4%

Figure 3. Investigator-Assessed PFS in Patients Aged ≥80 Years



[a]95% CI values.

CI, confidence interval; PFS, progression-free survival.

- Overall, 6/38 (15.8%) of patients had received subsequent anti-cancer therapy and 10/38 (26.3%) of patients had died without initiating subsequent therapy
- At 36 and 72 months, an estimated 94.5% (95% CI; 79.8, 98.6) and 87.7% (95% CI; 70.2, 95.3) of patients, respectively, had not initiated subsequent therapy
- Estimated overall survival rate at 36 and 72 months was 86.8% (95% CI; 71.2, 94.3) and 75.8% (95% CI; 58.6, 86.6)

Safety

- In this ≥80 years subgroup analysis, treatment-emergent adverse events (TEAEs) of interest (any grade) included atrial fibrillation/flutter (15.8%), major hemorrhage (21.1%), hypertension (28.9%), and Grade ≥3 infections (36.8%), and second primary malignancy (excluding non-melanoma skin cancer) (15.8%). These rates are consistent with that seen in the ITT population adjusting for age
- The incidence of first onset TEAE and discontinuation due to TEAEs in the first 3 years, along with exposure-adjusted incidence rates, are shown in **Table 2**

Table 2. Onset of TEAE, Discontinuation Due to TEAE and EAIR, and Post-Treatment AEs

Event, n (%)	Incidence of first onset TEAE 0-3 years N=38	EAIR persons per 100 person-months[a]
Atrial fibrillation and flutter	2 (5.3)	0.26
Major hemorrhage	3 (7.9)	0.36
Hypertension	8 (21.1)	0.56
Grade ≥3 infections	8 (21.1)	0.68
SPM (excluding NMSC)	2 (5.3)	0.31
Discontinuation due to any TEAE	3 (7.9)	–

[a]EAIR was calculated as the number of patients having the TEAE category divided by the total time from the first dose date to the first event date, or the exposure time if there is no event.

EAIR, exposure-adjusted incidence rate; NMSC, non-melanoma skin cancer; SPM, second primary malignancy; TEAE, treatment-emergent adverse event.

REFERENCES

1. Zoni-Berisso M, et al. *Clin Epidemiol.* 2014;6:213-220.
2. Go AS, et al. *JAMA*. 2001;285(18):2370-2375.
3. Tam, C, et al. *Blood*. 2025;146(Suppl 1):2129.
4. Tam CS, et al. *Lancet Oncol.* 2022;23(8):1031-1043.

DISCLOSURES

AT: Consulting or advisory role for AstraZeneca, AbbVie, BeOne, J&J, Lilly; speakers' bureau for AbbVie, BeOne, J&J, Lilly. **AO**: Nothing to disclose. **TM**: Consulting or advisory roles for Janssen-Cilag, AstraZeneca, BeOne, SOBI, Roche, AbbVie, Alexion Pharmaceuticals, and Lilly; speakers' bureau participation for AbbVie, Janssen-Cilag, Gilead Sciences, Alexion Pharmaceuticals, AstraZeneca, and SOBI; research support from AbbVie, Janssen-Cilag; and travel, accommodations, or expenses from Janssen-Cilag, AbbVie, Alexion Pharmaceuticals, and AstraZeneca. **ML**: Employment and equity holder in Roche, BeOne Medicines, Ltd. **JS**, **WA**: Employment and equity holder in BeOne Medicines, Ltd. **JH**: Employment in BeOne Medicines, Ltd., Genentech; equity holder in BeOne Medicines, Ltd., Roche. **CST**: Honoraria from Janssen, AbbVie, BeOne Medicines, Ltd, Lilly, AstraZeneca, Gilead, Merck; research support from AbbVie, Janssen, BeOne Medicines, Ltd.

ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was funded by BeOne Medicines, Ltd. Editorial assistance was provided by SNELL Medical Communication Inc.

CORRESPONDENCE: Alessandra Tedeschi, alessandra.tedeschi@ospedaleniguarda.it

Presented at EHA 2026; June 11-14, 2026, Stockholm, Sweden