Select Adverse Events of Interest With Zanubrutinib vs Fixed-Duration Combination of Venetoclax + Obinutuzumab in Treatment-Naive Chronic Lymphocytic Leukemia

CLL-483

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CONCLUSIONS

- Rates of TEAEs leading to discontinuation and rates of AEs of interest, including infections (excluding COVID-19), were proportionately lower with zanubrutinib compared with VenO, with a median treatment duration of 23.9 months
- Incidence of hematologic grade 3/4 AEs was lower with zanubrutinib vs VenO in this analysis
- Despite a much longer median treatment duration with zanubrutinib, EAIRs across different TEAE categories were significantly lower than those with VenO
- Continuous zanubrutinib monotherapy does not appear to increase the risk of infection compared with fixed-duration VenO, even with longer treatment duration

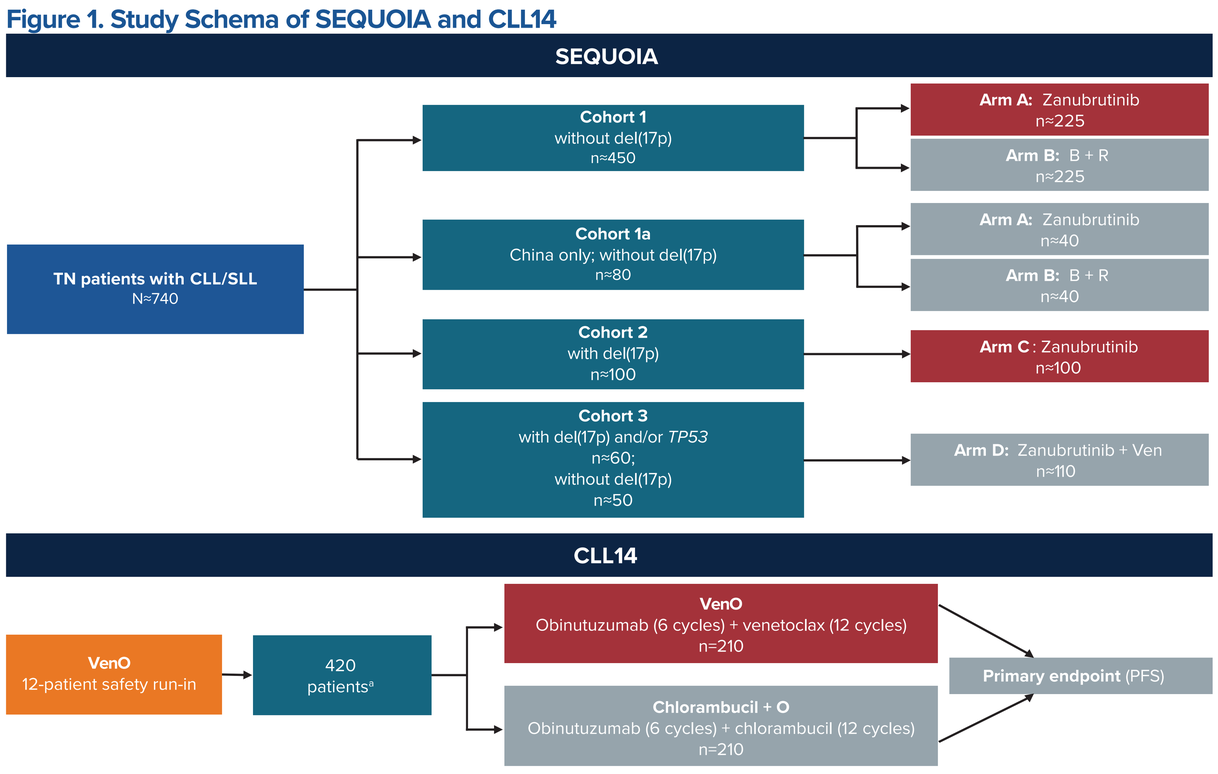
INTRODUCTION

- Multiple treatment regimens are available for effectively managing treatment-naive (TN) patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)[1]
  - These regimens target different B-cell signaling pathways and may differ by treatment exposure (continuous vs fixed-duration treatment); therefore, understanding the safety profile of these regimens is critical to optimizing patient outcomes
- The efficacy and safety of continuous monotherapy with the Bruton tyrosine kinase inhibitor zanubrutinib have been evaluated in TN patients with CLL/SLL in the phase 3 SEQUOIA (NCT03336333) trial,[2,3] while the combination of fixed-duration treatment with the B-cell lymphoma 2 inhibitor venetoclax plus the anti-CD20 monoclonal antibody obinutuzumab (VenO) was evaluated in CLL14 (NCT02242942)[4,5]
- In the absence of head-to-head clinical trials comparing zanubrutinib and VenO, an indirect analysis of safety outcomes was conducted in patients with CLL/SLL treated with zanubrutinib in SEQUOIA and VenO in CLL14

METHODS

- Safety outcomes with zanubrutinib monotherapy vs VenO were compared between SEQUOIA and CLL14; safety outcomes included treatment-emergent adverse events (TEAEs), TEAEs of interest, which included grade 3 or 4 infections, neutropenia, febrile neutropenia, thrombocytopenia, and TEAEs leading to treatment discontinuation
- The study schema for SEQUOIA and CLL14 is shown in **Figure 1**
- For zanubrutinib, safety data from arms A and C of SEQUOIA (N=351), at a median treatment duration of 23.9 months (to match safety follow-up for VenO) and 61.2 months, were used[2,3]
- For VenO, safety data from available publications of the fixed-duration VenO arm (N=212), at a median treatment duration of 11.1 months, were evaluated[4,5]
- Zanubrutinib infection outcomes were adjusted for COVID-19, as SEQUOIA was ongoing during the pandemic; CLL14 was conducted prior to the pandemic

Figure 1. Study Schema of SEQUOIA and CLL14



[a]Includes patients with or without del(17p) or *TP53* mutation.
Abbreviations: B, bendamustine; CLL, chronic lymphocytic leukemia; O, obinutuzumab; PFS, progression-free survival; R, rituximab; SLL, small lymphocytic lymphoma; TN, treatment naive; Ven, venetoclax; VenO, venetoclax plus obinutuzumab.

RESULTS

Baseline Characteristics

- Overall, baseline characteristics in the intent-to-treat populations of SEQUOIA and CLL14 were similar, except Cumulative Illness Rating Scale (CIRS) score, creatine clearance of <70 mL/min, Binet stage, and del(17p) status (**Table 1**)
  - In CLL14, patients with coexisting conditions were enrolled, as determined by a CIRS score of >6 and creatinine clearance of <70 mL/min

Table 1. Baseline Demographics and Patient Characteristics (ITT Population)

	SEQUOIA Zanubrutinib N=352	CLL14 VenO N=216
Age, median (range), years	70 (40-87)	72 (43-89)
Age ≥75 years, %	26.7	33.3
Male, %	66.2	67.6
White, %	92.6	98.0
ECOG PS 0-1, %	91.8	87.0
CIRS score >6, %	25.4	86.1
Creatinine clearance, median, mL/min	70	65.2
Creatinine clearance <70 mL/min, %	48.3	59.5
Time from initial diagnosis, median (range), months	29 (0.7-323.8)	31.2 (0.4-214.7)
Binet stage at study entry for CLL, %		
A	13.7	21.3
B	54.5	35.6
C	31.8	43.1
del(17p), %	31.8	8.1
***TP53* mutation, %**	18.2	12.0
del(11q), %	11.6	17.1
del(13q), %	28.1	33.8

Abbreviations: CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; VenO, venetoclax plus obinutuzumab.

Safety Outcomes

- Median treatment durations differed between SEQUOIA and CLL14 due to continuous vs fixed-duration study designs (**Table 2**)
  - Median treatment duration was 12.0, 23.9, and 61.2 months at selected data cutoffs with zanubrutinib vs 11.1 months with VenO
- Serious TEAEs, TEAEs leading to death, and TEAEs leading to discontinuation were proportionately lower at earlier cutoffs with zanubrutinib and comparable at 62.7 months with zanubrutinib vs VenO (**Table 2**)

Table 2. Overall Summary of Adverse Events (Safety Population)

	SEQUOIA Zanubrutinib (N=351)[a]			CLL14 VenO (N=212)	
	≤52 weeks	≤104 weeks	Overall period[a]	≤154 weeks	Median, 170 weeks
Treatment duration, median, months	12.0	23.9	61.2	11.1[b]	11.1[b]
Follow-up time, median, months	12.0[c]	23.9[c]	62.7	28.1	39.7
Any-grade TEAEs, n (%)	322 (91.7)	332 (94.6)	338 (96.3)	200 (94.3)	201 (94.8)
Grade 3/4 AEs, n (%)	132 (37.6)	169 (48.1)	226 (64.4)	167 (78.8)[d]	150 (70.8)[d]
Neutropenia	27 (7.7)	32 (9.1)	36 (10.3)	112 (52.8)	112 (52.8)
Neutrophil count decreased	9 (2.6)	10 (2.8)	10 (2.8)	9 (4.2)	9 (4.2)
Thrombocytopenia	4 (1.1)	4 (1.1)	6 (1.7)	29 (13.7)	29 (13.7)
Febrile neutropenia	2 (0.6)	2 (0.6)	3 (0.9)	11 (5.2)	11 (5.2)
Any serious TEAEs, n (%)	83 (23.6)	124 (35.3)	200 (57.0)	104 (49.1)	115 (54)
TEAEs leading to death, n (%)[e]	5 (1.4)	13 (3.7)	27 (7.7)	16 (7.5)	19 (9.0)
TEAEs leading to discontinuation, n (%)	14 (4.0)	26 (7.4)	66 (18.8)	33 (15.6)	33 (15.6)

[a]Data cutoff date was April 30, 2024. [b]Treatment duration range was 0 to 14.1 months. [c]The median follow-up time for each interval is calculated from first dose date until interval end date or to the last dose date if discontinued earlier. [d]Data are inconsistent between the 2019[4] (median follow-up, 28.1 months) and 2020[5] (median follow-up, 37.9 months) publications. Grade 3/4 AEs were reported in 78.8% (EAIR, 0.0710) of patients in the 2019 publication, but this number decreased to 70.8% (EAIR, 0.0637) as the median follow-up time increased to 39.7 months in the 2020 publication. [e]The most frequent AEs leading to death in the zanubrutinib cohort were COVID-19, COVID-19 pneumonia, and pneumonia; in the VenO cohort, the most common AEs leading to death were sepsis and second primary malignancies.
Abbreviations: AE, adverse event; EAIR, exposure-adjusted incidence rate; TEAE, treatment-emergent adverse event; VenO, venetoclax plus obinutuzumab.

- Exposure-adjusted incidence rates (EAIRs) across different TEAE categories were lower with zanubrutinib vs VenO (**Table 3**)

Table 3. Overall Summary of Adverse Events: Exposure-Adjusted Incidence Rates (Safety Population)[a]

	SEQUOIA Zanubrutinib (N=351)			CLL14 VenO (N=212)	
	≤52 weeks	≤104 weeks	Overall period[b]	≤154 weeks	Median, 170 weeks
Treatment duration, median, months	12.0	23.9	61.2	11.1[c]	11.1[c]
Follow-up time, median, months	12.0[d]	23.9[d]	62.7	28.1	39.7
Any-grade TEAEs	7.64	3.96	1.57	8.50	8.54
Grade 3/4 AEs	3.13	2.01	1.05	7.10	6.37
Neutropenia	0.64	0.38	0.17	4.76	4.76
Neutrophil count decreased	0.21	0.12	0.05	0.38	0.38
Thrombocytopenia	0.09	0.05	0.03	1.23	1.23
Febrile neutropenia	0.05	0.02	0.01	0.47	0.47
Any serious TEAEs	1.97	1.48	0.93	4.42	4.89
TEAEs leading to death	0.12	0.15	0.13	0.68	0.81
TEAEs leading to discontinuation	0.33	0.31	0.31	1.40	1.40

[a]EAIR is calculated as [n/(N × median treatment duration)] × 100; units for EAIR data are per 100 patient-months. [b]Data cutoff date was April 30, 2024. [c]Treatment duration range was 0 to 14.1 months. [d]The median follow-up time for each interval is calculated from first dose date until interval end date or to the last dose date if discontinued earlier.
Abbreviations: AE, adverse event; EAIR, exposure-adjusted incidence rate; TEAE, treatment-emergent adverse event; VenO, venetoclax plus obinutuzumab.

- With a longer median follow-up of 62.7 months, zanubrutinib was associated with significantly lower rates of the AEs of interest compared with VenO with median follow-up of 39.7 months, except grade 3/4 infections (**Table 4**)
  - With zanubrutinib vs VenO, the incidence of grade 3/4 infections (excluding COVID-19; 11.1% vs 17.5%), neutropenia (9.1% vs 52.8%), thrombocytopenia (1.1% vs 13.7%), febrile neutropenia (0.6% vs 5.2%), and TEAEs leading to discontinuation (7.4% vs 15.6%) were lower at the 23.9-month median treatment duration with zanubrutinib (P<.05 for all)
  - At the 61.2-month median treatment duration with zanubrutinib, the incidence rate of infection was higher with zanubrutinib (27.1%) vs VenO (17.5%) (P=.010) but similar after excluding COVID-19 (20.2% vs 17.5%; P=.418)
- Rates of grade 3/4 infections, excluding COVID-19, in patients treated with zanubrutinib for up to 4 years were similar to those in patients treated with VenO for 1 year (**Table 5**)

Table 4. Adverse Events of Interest With Zanubrutinib vs VenO (Safety Population)

	SEQUOIA Zanubrutinib (N=351)	CLL14 VenO (N=212)	OR (95% CI), P value	SEQUOIA Zanubrutinib[a] (N=351)	CLL14 VenO (N=212)	OR (95% CI), P value
Treatment duration, median, months	23.9	11.1[b]	–	61.2	11.1	–
Follow-up time, median, months	23.9	39.7	–	62.7	39.7[c]	–
Grade 3/4 AEs of interest, n (%)						
Neutropenia	32 (9.1)	112 (52.8)	0.09 (0.06-0.14), P<.001	36 (10.3)	112 (52.8)	0.10 (0.07-0.16), P<.001
Thrombocytopenia	4 (1.1)	29 (13.7)	0.07 (0.03-0.21), P<.001	6 (1.7)	29 (13.7)	0.11 (0.04-0.27), P=.001
Febrile neutropenia	2 (0.6)	11 (5.2)	0.10 (0.02-0.48), P=.004	3 (0.9)	11 (5.2)	0.16 (0.04-0.57), P=.005
Infections and infestations	44 (12.5)	37 (17.5)	0.68 (0.42-1.09), P=.109	95 (27.1)	37 (17.5)	1.76 (1.15-2.69), P=.010[b]
Excluding COVID-19	39 (11.1)	37 (17.5)	0.59 (0.36-0.96), P=.034	71 (20.2)	37 (17.5)	1.20 (0.77-1.86), P=.418[b]
Pneumonia	8 (2.3)	11 (5.2)	0.43 (0.17-1.08), P=.071	19 (5.4)	11 (5.2)	1.05 (0.49-2.24), P=.909
Sepsis	2 (0.6)	3 (1.4)	0.40 (0.07-2.41), P=.317	4 (1.1)	3 (1.4)	0.80 (0.18-3.62), P=.775
Any-grade AEIs leading to treatment discontinuation, n (%)	26 (7.4)	33 (15.6)	0.43 (0.25-0.75), P=.003	66 (18.8)	33 (15.6)	1.26 (0.79-1.99), P=.329

[a]Data cutoff date was April 2024. [b]Treatment duration range was 0 to 14.1 months. [c]Based on Fischer et al 2019,[3] as data from Al-Sawaf et al 2020[4] were missing.
Abbreviations: AE, adverse event; AEI; adverse event of interest; OR, odds ratio; VenO, venetoclax plus obinutuzumab.

Table 5. Grade 3/4 Infections Over Time (Safety Population)

		SEQUOIA Zanubrutinib (N=351)[2,3]								CLL14 VenO (N=212)[4,5]
		≤52 weeks	≤60 weeks	≤88 weeks	≤104 weeks	≤156 weeks	≤208 weeks	≤234 weeks	Overall[a]	≤154 weeks
Treatment duration, median, months		12.0	13.8	20.2	23.9	35.9	47.8	53.8	61.2	11.1
Follow-up time, median, months		12.0[b]	13.8[b]	20.2[b]	23.9[b]	35.9[b]	47.8[b]	53.8[b]	62.7	28.1
Grade 3/4 infection, excluding COVID-19	**n (%)**	29 (8.3)	31 (8.8)	38 (10.8)	39 (11.1)	49 (14.0)	56 (16.0)	64 (18.2)	71 (20.2)	37 (17.5)
	EAIR[c]	0.69	0.64	0.54	0.46	0.39	0.33	0.34	0.33	1.57

[a]Data cutoff date was April 2024. [b]The median follow-up time for each interval is calculated from first dose date until interval end date or to the last dose date if discontinued earlier. [c]EAIR is calculated as [n/(N × median treatment duration)] × 100; units for EAIR data are per 100 patient-months.
Abbreviations: EAIR, exposure-adjusted incidence rate; VenO, venetoclax plus obinutuzumab.

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DISCLOSURES

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