# Zanubrutinib (Zanu) vs Bendamustine + Rituximab (BR) in Patients (Pts) With Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL): Extended Follow-Up of the SEQUOIA Study

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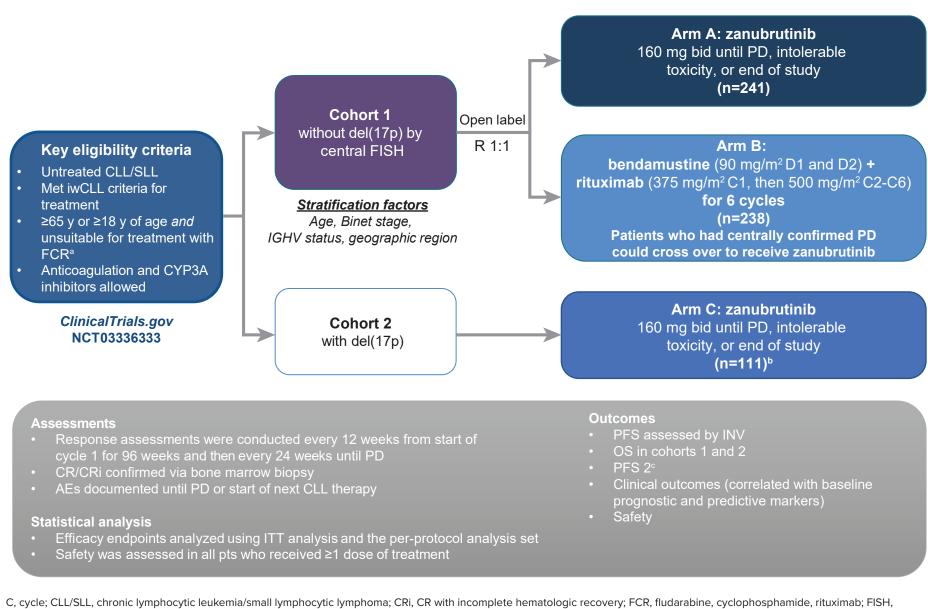
# BACKGROUND

- BTK inhibitors have transformed the therapeutic landscape for CLL/SLL by demonstrating prolonged PFS and OS over chemoimmunotherapy, the traditional standard of care<sup>1</sup>
- Zanubrutinib, a next-generation BTK inhibitor designed to minimize off-target binding and limit associated side effects,<sup>2</sup> is approved in the US,<sup>3</sup> EU,<sup>4</sup> and China<sup>5</sup> for CLL/SLL
- Results from the SEQUOIA study (NCT03336333), at a median follow-up of 26.2 months, demonstrated superior PFS in treatment-naive patients with CLL/SLL without del(17p) who received zanubrutinib vs BR (HR, 0.42; 95% Cl, 0.28-0.63; 2-sided P<.0001); results were similar in treatment-naive patients with del(17p) who received zanubrutinib monotherapy<sup>6</sup>
- An independent data monitoring committee determined that the SEQUOIA study met its primary endpoint at the interim analysis<sup>6</sup>
- Here, we report the updated efficacy and safety results from the SEQUOIA study after approximately 18 months of additional follow-up (data cutoff: 31 October 2022)

# METHODS

Figure 1. Study Design

• Methodological details have been published<sup>6</sup> and are summarized in Figure 1



fluorescence in situ hybridization; IGHV, immunoglobulin heavy variable; INV, investigator; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; pt, patient. <sup>a</sup> Defined as Cumulative Illness Rating Scale >6, creatinine clearance <70 mL/min, or a history of previous severe infection or multiple infections within the last 2 years; <sup>b</sup> One patient without del(17p) was misassigned to the nonrandomly assigned cohort of patients with del(17p). The patient is excluded from the efficacy analysis in this cohort; <sup>c</sup> Defined as the time from randomization to death or the date of progression on the next line of therapy subsequent to study treatment.

# RESULTS

#### Patients

- As of 31 October 2022, 479 patients without del(17p) had been randomized to receive zanubrutinib (n=241) or BR (n=238), and 111 patients with del(17p) received zanubrutinib monotherapy; 180 patients (74.7%) without del(17p) and 78 patients (70.3%) with del(17p) were still receiving zanubrutinib
- The median follow-up was 43.7 months (range, 0-60.0 months) in cohort 1 and 47.9 months (range, 5.0-56.9 months) in cohort 2

- progression
- treatment groups (**Table 1**)

### Age, median (ran Age ≥65 years, n Male, n (%) ECOG PS 2, n (%)

**Geographic regio** 

North America	
Europe	

Asia-Pacific Binet stage C, n ( Bulky disease ≥5

Cytopenia at base

**Unmutated IGHV**,

del(11q), n (%) TP53 mutation, n

Complex karyoty  $\geq$ 3 abnormalities,

BR, bendamustine plus rituximab; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy variable; SLL, small lymphocytic lymphoma

### Efficacy

- (Figure 2A)
- 50.0%, respectively
- (Figure 2B)

- CRi rate was 14.5%

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> • In arm B, 188 patients (79.0%) completed their BR regimen, 86 (36.1%) had progression irrespective of completing the full 6 cycles, and 41 (17.2%) crossed over to receive zanubrutinib after centrally confirmed disease

• Zanubrutinib discontinuation rates in patients without and with del(17p) were 24.9% and 29.7%, respectively

• Baseline demographics and disease characteristics were similar across

 Table 1. Patient Characteristics and Baseline Demographics

		5 1		
	Patients without del(	Patients with del(17p)		
	Arm A: zanubrutinib (n=241)	Arm B: BR (n=238)	Arm C: zanubrutinib (n=111)ª	
ige), years	70 (40-86)	70 (35-87)	71 (42-87)	
<b>(%)</b> <sup>b</sup>	198 (82)	195 (82)	95 (86)	
	154 (64)	144 (61)	79 (71)	
	15 (6)	20 (8)	14 (13)	
on, n (%)				
	34 (14)	28 (12)	12 (11)	
	174 (72)	172 (72)	52 (47)	
	33 (14)	38 (16)	47 (42)	
(% <b>)</b> <sup>c</sup>	70 (29)	70 (29)	39 (35)	
cm, n (%)	69 (29)	73 (31)	44 (40)	
eline, n (%) <sup>d</sup>	102 (42)	110 (46)	61 (55)	
∕, n/N (%)⁰	125/234 (53)	121/231 (52)	67/103 (65)	
	43 (18)	46 (19)	37 (33)	
n/N (%)	15/232 (6)	13/223 (6)	47/109 (43)	
pe with , n/N (%) <sup>f</sup>	23/164 (14)	22/161 (14)	33/88 (38)	

<sup>a</sup> One patient without del(17p) was misassigned to the nonrandomly assigned cohort of patients with del(17p). The patient is excluded from the efficacy analysis in this cohort; <sup>b</sup> Patients aged ≥75 years included 63 patients in group A (26%), 53 patients in group B (22%), and 27 patients in group C (24%); <sup>c</sup> Patients with SLL had Binet stage calculated as if they had CLL; <sup>d</sup> Defined as having anemia (hemoglobin <110 g/L), thrombocytopenia (platelets <100×10<sup>9</sup>/L), or neutropenia (absolute neutrophil count <1.5×10<sup>9</sup>/L); <sup>e</sup> Twenty-two patients had insufficient RNA quantity/quality for polymerase chain reaction amplification of immunoglobulin heavy chain variable region for sequencing or had missing data; <sup>f</sup> Patients with missing/insufficient metaphase activity were omitted from the complex karyotype analysis.

• In cohort 1, median PFS was not reached in patients who received zanubrutinib; in patients who received BR, median PFS was 42.2 months

- Estimated 42-month PFS rates with zanubrutinib and BR were 82.4% and

• PFS was significantly improved with zanubrutinib vs BR in patients with mutated IGHV (2-sided P=.00033) and unmutated IGHV (2-sided P<.0001)

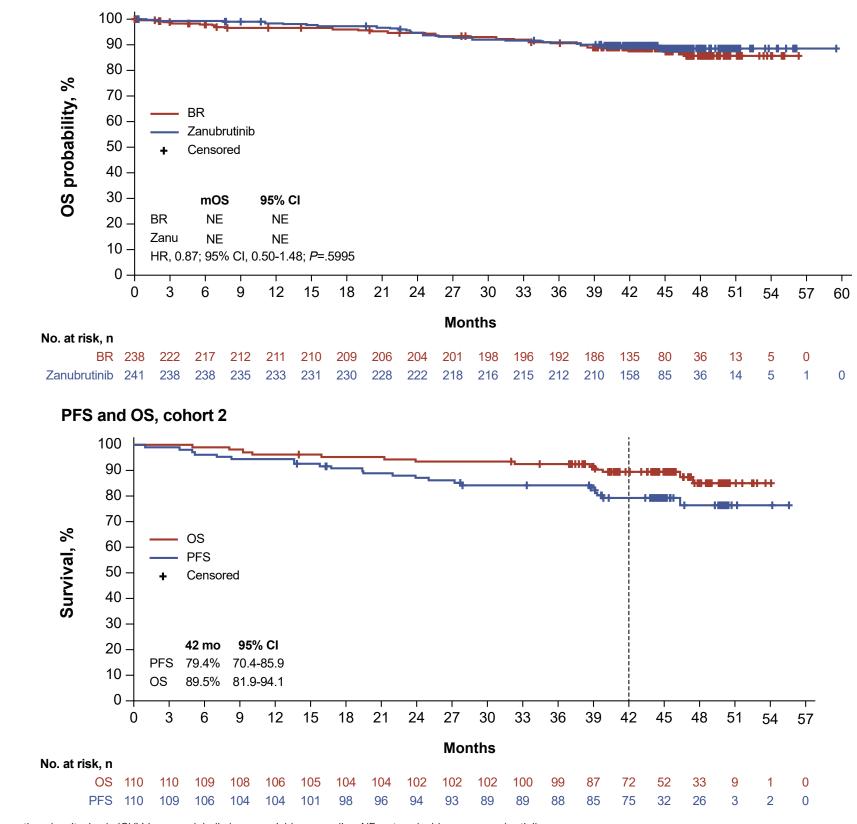
 CR/CR with incomplete hematologic recovery (CRi) rates in patients without del(17p) who received zanubrutinib vs BR were 17.4% vs 21.8%, respectively

• Median OS was not reached in either group; the estimated 42-month OS rates were 89.4% and 88.3%, respectively (**Figure 2C**)

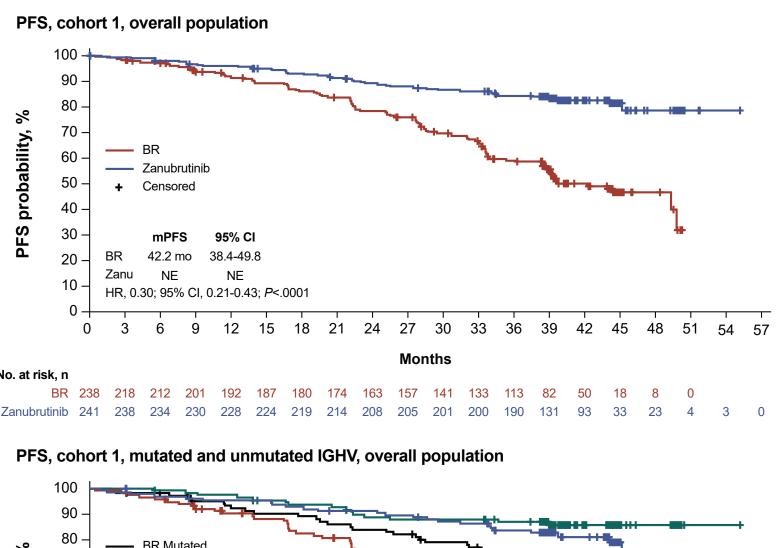
• In cohort 2, the median PFS and OS were not reached; the estimated 42-month rates were 79.4% and 89.5%, respectively (Figure 2D), and the CR/

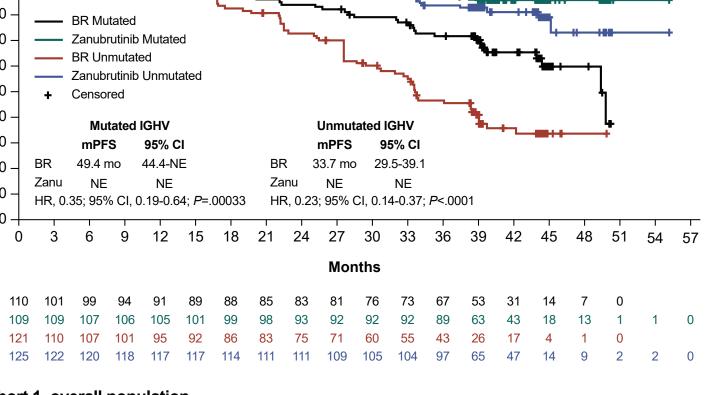
#### Figure 2. PFS and OS in Cohort 1 [Without del(17p)] and Cohort 2 [With del(17p)]<sup>a</sup>

PFS, cohort 1, overall population ----- Zanubrutinib Censored No. at risk, n BR 238 218 212 201 192 187 180 174 163 157 141 133 113 82 50 18 8 0 , cohort 1, mutated and unmutated IGHV, overall population BR Mutated — Zanubrutinib Mutated BR Unmutated —— Zanubrutinib Unmutated Mutated IGH mPFS 95% C 49.4 mo 44.4-NE Zanu NF NF HR, 0.35; 95% CI, 0.19-0.64; P=.00033 HR, 0.23; 95% CI, 0.14-0.37; P<.0001 No. at risk, n BR Mutated 110 101 99 94 91 89 88 85 83 81 76 73 67 53 31 14 7 0 109 107 106 105 101 99 98 93 92 92 92 89 BR Unmutated 121 110 107 101 95 92 86 83 75 71 60 55 43 26 17 4 1 Zanubrutinib Unmutated 125 122 120 118 117 117 114 111 111 109 105 104 97 65 47 14 9 2 2 cohort 1, overall populatior



BR, bendamustine plus rituximab; IGHV, immunoglobulin heavy variable; m, median; NE, not evaluable; zanu, zanubrutinib <sup>a</sup> All *P* values are 2-sided.





### Safety

- AEs of interest (AEIs) in patients without del(17p) receiving zanubrutinib vs BR and in patients with del(17p) are shown in **Table 2**
- Exposure-adjusted incidence rates for hypertension were similar between arms and lower than previously reported (**Table 3**)

#### Table 2. Treatment-Emergent and Posttreatment AEIs<sup>a</sup> in Cohorts 1 and 2 (Any Grade and Grade ≥3)<sup>b</sup>

	Patients without del(17p)			Patients with del(17p)		
	Arm A: zanubrutinibArm B: BR (n=240)a(n=240)a(n=227)b		Arm C: zanubrutinil (n=111)			
AEIs, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Infections	175 (72.9)	57 (23.8)	142 (62.6)	50 (22.0)	89 (80.2)	30 (27.0)
Bleeding	117 (48.8)	14 (5.8)	28 (12.3)	4 (1.8)	64 (57.7)	6 (5.4)
Other malignancies	45 (18.8)	22 (9.2)	28 (12.3)	11 (4.8)	27 (24.3)	8 (7.2)
Hypertension	42 (17.5)	22 (9.2)	31 (13.7)	15 (6.6)	15 (13.5)	7 (6.3)
Diarrhea	41 (17.1)	4 (1.7)	32 (14.1)	5 (2.2)	22 (19.8)	1 (0.9)
Neutropenia	40 (16.7)	30 (12.5)	129 (56.8)	116 (51.1)	21 (18.9)	18 (16.2)
Arthralgia	37 (15.4)	2 (0.8)	23 (10.1)	1 (0.4)	26 (23.4)	1 (0.9)
Anemia	17 (7.1)	1 (0.4)	47 (20.7)	5 (2.2)	7 (6.3)	0 (0)
Thrombocytopenia	15 (6.3)	5 (2.1)	41 (18.1)	18 (7.9)	9 (8.1)	2 (1.8)
Atrial fibrillation/flutter	12 (5.0)	3 (1.3)	6 (2.6)	3 (1.3)	7 (6.3)	5 (4.5)
Myalgia	9 (3.8)	0 (0)	4 (1.8)	0 (0)	8 (7.2)	1 (0.9)
Opportunistic infection	6 (2.5)	1 (0.4)	4 (1.8)	3 (1.3)	1 (0.9)	1 (0.9)

<sup>a</sup> Patients who did not receive zanubrutinib are not included in the safety analysis; <sup>b</sup> Patients who did not receive BR are not included in the safety analysis

#### Table 3. Summary of EAIRs<sup>a</sup> for Select AEIs

	Patients without del(	Patients with del(17p)	
	Arm A: zanubrutinib (n=240) <sup>b</sup>	Arm B: BR (n=227)°	Arm C: zanubrutinib (n=111)
Atrial fibrillation and flutter	0.13	0.08	0.15
Hemorrhage	2.02	0.40	2.73
Major hemorrhage	0.20	0.05	0.20
Hypertension	0.49	0.45	0.35

AEI, AE of interest: BR, bendamustine plus rituximab; EAIR, exposure-adjusted incidence rate. <sup>a</sup> EAIR was calculated as the number of patients with an event in each TEAE category divided by the total time from the first dose date to the first event date, or the exposure time if no event occurred: <sup>b</sup> Patients who did not receive zanubrutinib are not included in the safety analysis: <sup>c</sup> Patients who did not receive BR are not included in the safety analysis.

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## CONCLUSIONS

- The extended follow-up in the SEQUOIA study showed that the efficacy of zanubrutinib was maintained in previously untreated patients with CLL/SLL without del(17p) and that PFS rates were similar in patients with and without del(17p); OS rates were high in all arms of the trial
- Additionally, patients with mutated IGHV who received zanubrutinib demonstrated significant improvements in PFS with extended follow-up vs those who received BR; patients with unmutated IGHV who received zanubrutinib maintained the PFS benefit vs patients who received BR that was observed at the interim analysis
- Zanubrutinib was well tolerated over this extended treatment period and aligned with the known profile of BTK inhibitors; atrial fibrillation events remained low
- The results of this extended follow-up in the SEQUOIA study support the use of zanubrutinib as a valuable first-line treatment option for elderly patients with CLL/SLL and those with del(17p)

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### DISCLOSURES

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