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Zanubrutinib in the Treatment of Patients With del(17p) and/or *TP53* CLL/SLL: Analysis Across Clinical Studies[1]

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Introduction

Patients with CLL/SLL with del(17p) and/or *TP53* mutations represent a high-risk population with a historically poor prognosis

Zanubrutinib, a highly potent and selective BTKi, has been evaluated in patients with CLL/SLL, including those with del(17p) and/or *TP53*-mutated CLL/SLL, in various clinical studies such as SEQUOIA (NCT03336333), ALPINE (NCT03734016), and AU-003 (NCT02343120)

Data from TN and R/R patients with CLL/SLL who harbor del(17p) and/or *TP53* mutations in **SEQUOIA**, **ALPINE**, and **AU-003** were analyzed—the largest evaluation to date in this population—to assess the efficacy and safety of zanubrutinib

Methods

	SEQUOIA (N=127)[a]	ALPINE (N=150)	AU-003 (N=24)
Patient population	TN CLL or SLL with del(17p) and/or *TP53* mutations	R/R CLL or SLL with del(17p) and/or *TP53* mutations	TN or R/R CLL or SLL with del(17p) and/or *TP53* mutations
Treatments	Zanubrutinib	Zanubrutinib vs ibrutinib	Zanubrutinib
Median follow-up	64.8 months	38.9 months	69.6 months
Endpoints assessed[b]	PFS, OS, response rates, TEAEs		
Statistical analysis	• Estimates for PFS and OS were calculated using Kaplan-Meier methods • PFS/OS adjustments were made to account for the potential impact of the COVID-19 pandemic, given its overlap with the study periods • For ALPINE only, HRs and 95% CIs were estimated for zanubrutinib versus ibrutinib		

[a]Included patients with del(17p) who were misassigned (n=2) patients with del(17p) and/or *TP53* mutations from the non-del(17p) zanubrutinib study arm who had these mutations identified after the initiation of the study (n=15). [b]PFS, OS, and response rate (defined as PR- L or better) were assessed by investigators; in ALPINE, disease response and PFS were also assessed by an IRC.

Baseline Characteristics

A total of 301 patients (TN=132, R/R=169) with CLL/SLL and del(17p) and/or *TP53* mutations were included

	SEQUOIA	ALPINE		AU-003	
	Zanubrutinib	Zanubrutinib	Ibrutinib	Zanubrutinib	
Study population	TN (N=127)[a]	R/R (n=75)	R/R (n=75)	TN (n=5)	R/R (n=19)
Complex karyotype, n/N (%)[b]	32/89 (36.0)	14/37 (37.8)	24/47 (51.1)	Not specified	Not specified
TP53 mutations, n (%)	62 (48.8)	50 (66.7)	45 (60.0)	3 (60.0)	11 (57.9)
del(17p), n (%)	112 (88.2)	45 (60.0)	50 (66.7)	3 (60.0)	13 (68.4)

[a]Included patients with del(17p) who were misassigned (n=2) patients with del(17p) and/or *TP53* mutations from the non-del(17p) zanubrutinib study arm who had these mutations identified after the initiation of the study (n=15). [b]Complex karyotype defined as having ≥3 abnormalities.

Results

Among TN patients with del(17p) and/or *TP53* mutations in SEQUOIA, median PFS-INV and OS-INV were not reached

Outcomes	Median	Estimated 60-month rate	COVID-19–adjusted 60-month rate
PFS	NR	70.7% (95% CI, 61.5-78.1)	72.2% (95% CI, 63.0-79.4)
OS	NR	82.3%	84.7%

Among R/R patients with del(17p) and/or *TP53* mutations in ALPINE, zanubrutinib demonstrated longer PFS by IRC compared with ibrutinib; median OS was not reached in either treatment group

Outcomes	Median	Estimated 36-month rate	COVID-19–adjusted 36-month rate
PFS			
Zanubrutinib	50.2 months (95% CI, 33.1-NE)	59.3% (95% CI, 46.9-69.6)	63.7% (95% CI, 51.0-73.8)
Ibrutinib	28.0 months (95% CI, 22.2-38.7)	41.6% (95% CI, 29.6-53.1)	43.1% (95% CI, 30.8-54.8)
OS			
Zanubrutinib	NR	73.6% (95% CI, 61.8-82.3)	78.8% (95% CI, 67.2-86.6)
Ibrutinib	NR	72.5% (95% CI, 60.6-81.3)	74.8% (95% CI, 63.0-83.4)

Evaluation of PFS by IRC was consistent with PFS assessed by investigators

Among the patients with del(17p) and/or *TP53* mutations in AU-003, median PFS-INV was 61.4 months

Outcomes	Median	Estimated 60-month rate
PFS	61.4 months	50.6% (95% CI, 24.6-71.8)
OS	NR	Not specified

Among the 5 TN patients, 4 remained progression-free at 60 months

- Investigator-assessed response rates were 96.9% (95% CI, 95.2-98.8), 89.3% (95% CI, 80.1-95.3), and 88% for patients with del(17p) and/or *TP53* mutations in **SEQUOIA**, **ALPINE**, and **AU-003** trials, respectively
- Similar PFS was observed for TN patients regardless of complex karyotype, whereas in R/R patients, shorter PFS was observed in patients with complex karyotype compared with patients without complex karyotype

Non-Hematologic TEAEs and AESI in Patients With del(17p) and/or *TP53* Mutations

	SEQUOIA	ALPINE		AU-003
Non-hematologic TEAEs (Any grade, >20%)[a]	Zanubrutinib N=127[b]	Zanubrutinib n=75	Ibrutinib n=75	Zanubrutinib N=24
COVID-19	40 (31.5)	24 (32.4)	20 (26.7)	5 (20.8)
Upper respiratory tract infection	33 (26.0)	17 (23.0)	13 (17.3)	13 (54.2)
Arthralgia	30 (23.6)	9 (12.2)	11 (14.7)	5 (20.8)
Diarrhea	27 (21.3)	11 (14.9)	16 (21.3)	13 (54.2)
Contusion	26 (20.5)	11 (14.9)	4 (5.3)	8 (33.3)
AESI (All grade)[a]				
Infections Opportunistic infections	103 (81.1) 1 (0.8)	57 (77.0) 2 (2.7)	59 (78.7) 3 (4.0)	22 (91.7) 3 (12.5)
Hemorrhage Major hemorrhage	74 (58.3) 12 (9.4)	33 (44.6) 4 (5.4)	25 (33.3) 1 (1.3)	15 (62.5) 1 (4.2)
Second primary malignancies Skin cancers	37 (29.1) 27 (21.3)	10 (13.5) 6 (8.1)	8 (10.7) 5 (6.7)	9 (37.5) 5 (20.8)
Hypertension	23 (18.1)	16 (21.6)	18 (24.0)	1 (4.2)
Neutropenia	23 (18.1)	22 (29.7)	26 (34.7)	6 (25.0)
Anemia	11 (8.7)	13 (17.6)	16 (21.3)	4 (16.7)
Thrombocytopenia	10 (7.9)	11 (14.9)	11 (14.7)	4 (16.7)
Atrial fibrillation or flutter	9 (7.1)	3 (4.1)	12 (16.0)	4 (16.7)

[a]Events in this category are listed according to decreasing incidence in the SEQUOIA trial. [b]Included patients with del(17p) who were misassigned (n=2) patients with del(17p) and/or *TP53* mutations from the non-del(17p) zanubrutinib study arm who had these mutations identified after the initiation of the study (n=15).

The safety of zanubrutinib in high-risk CLL patients was consistent with that of previous studies in non–high-risk patients[2,3]

Limitations

1. Analyses are based on small numbers of subset populations from larger studies; SEQUOIA and AU-003 analyses were not prospectively defined and are considered exploratory
2. Cohort 2 of the SEQUOIA study, which formed the majority of data from the study employed in this analysis, and the AU-003 study were not randomized
3. Testing methodology for del(17p)/*TP53* mutations differed among the studies
4. Inconsistent definitions of high-risk CLL/SLL across BTKi studies limit comparison

Conclusions

- Zanubrutinib is a treatment option with an established safety profile in both TN and R/R CLL/SLL, with consistent PFS benefits regardless of del(17p) and/or *TP53* mutation status
- PFS is similar regardless of complex karyotype among patients with del(17p) and/or *TP53* CLL/SLL who received first-line zanubrutinib

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AESI, adverse event of special interest; BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; CLL, chronic lymphocytic leukemia; COVID-19, coronavirus disease 2019; del(17p), deletion of chromosome 17p; HR, hazard ratio; INV, investigator assessed; IRC, independent review committee; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival; PR-L, partial response with lymphocytosis; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TEAE, treatment-emergent adverse event; TN, treatment naive.

References: 1. Tam et al. *Blood Adv.* 2025 [Epub ahead of print]. **2.** Brown et al. *Blood.* 2024;144:2706-2717. **3.** Shadman et al. *J Clin Oncol.* 2025;43:780-787.