Extended Follow-Up of ALPINE Randomized Phase 3 Study Confirms Sustained Superior Progression-Free Survival With Zanubrutinib vs Ibrutinib for Treatment of R/R CLL/SLL

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INTRODUCTION

- Zanubrutinib is highly selective for Bruton tyrosine kinase (BTK) and has potent inhibitory activity against BTK[1]
- ALPINE, a randomized, multinational phase 3 study (NCT03734016) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL), established the superior efficacy of zanubrutinib over ibrutinib and confirmed the favorable safety and tolerability profile of zanubrutinib[2]
  - In a previous report at a median study follow-up of 29.6 months, zanubrutinib was clinically and statistically superior to ibrutinib (probability of progression-free survival [PFS] at 24 months: 78.4% vs 65.9%; HR, 0.65; 95% CI, 0.49-0.86; *P*=.0024)

METHODS

- The ALPINE study design has been described previously[2]
- This poster reports the results of an extended follow-up analysis (data cutoff: September 15, 2023)

RESULTS

Disposition

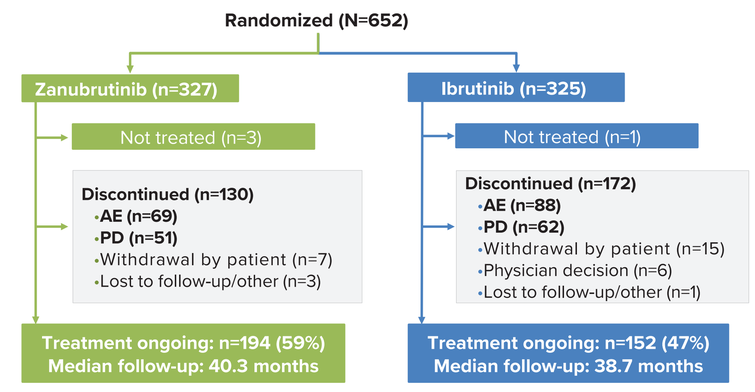
- Demographics and disease characteristics were balanced between groups (**Table 1**)
- At extended follow-up, 59% of zanubrutinib-treated patients and 47% of ibrutinib-treated patients had ongoing treatment (**Figure 1**)

Table 1. Demographics and Disease Characteristics

	Zanubrutinib (n=327)	Ibrutinib (n=325)
Age, median (range), years	67 (35-90)	68 (35-89)
≥65 years, n (%)	201 (61.5)	200 (61.5)
Male, n (%)	213 (65.1)	232 (71.4)
ECOG PS ≥1, n (%)	198 (60.6)	203 (62.5)
Prior no. of lines of systemic therapy, median (range)	1 (1-6)	1 (1-12)
>3 prior lines, n (%)	24 (7.3)	30 (9.2)
del(17p) and/or *TP53*^{mut}, n (%)	75 (22.9)	75 (23.1)
del(17p)	45 (13.8)	50 (15.4)
TP53^{mut} without del(17p)	30 (9.2)	25 (7.7)
IGHV mutational status, n (%)		
Mutated	80 (24.5)	70 (21.5)
Unmutated	240 (73.4)	241 (74.2)
Complex karyotype[a]	56 (17.1)	70 (21.5)
Bulky disease (≥5 cm), n (%)	145 (44.3)	149 (45.8)

Data cutoff: September 15, 2023.
[a] Complex karyotype is defined as having ≥3 abnormalities.
ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin variable heavy chain; *TP53*, tumor protein p53.

Figure 1. Patient Disposition at Extended Follow-Up

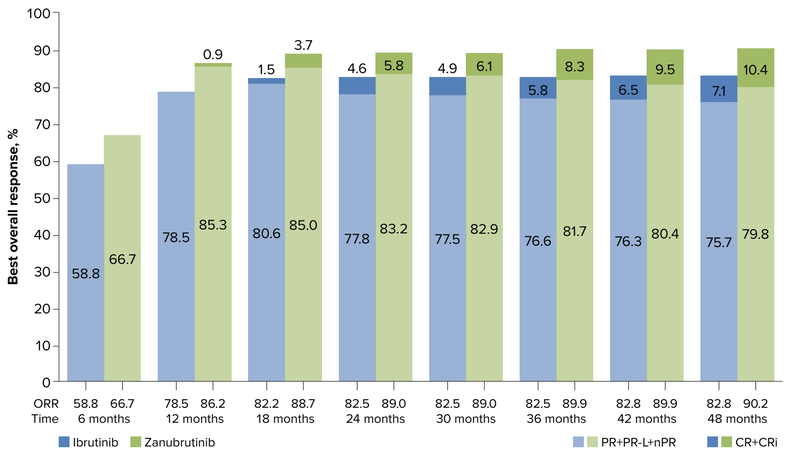


AE, adverse event; PD, progressive disease.

Efficacy

- A higher proportion of patients achieved complete response (CR)/complete response with incomplete hematologic recovery (CRi) with zanubrutinib than with ibrutinib (**Figure 2**)

Figure 2. Best Overall Response Over Time



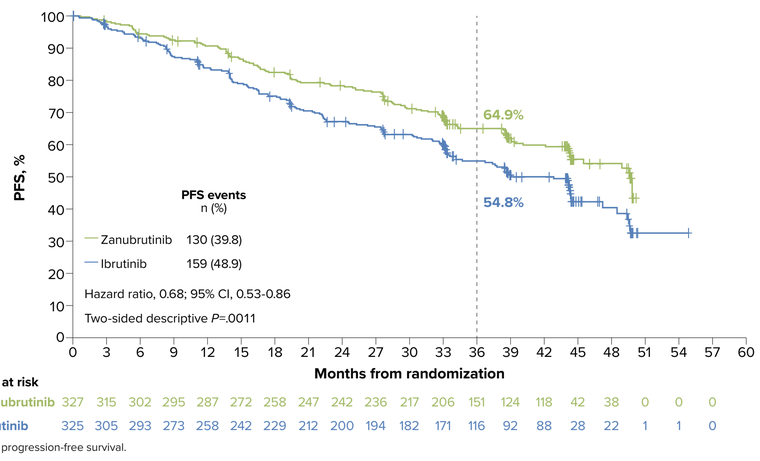
CR, complete response; CRi, complete response with incomplete hematologic recovery; ORR, objective response rate; PR, partial response; PR-L, partial response with lymphocytosis; nPR, nodular partial response.

CONCLUSIONS

- ALPINE is the only study to demonstrate PFS superiority in a head-to-head comparison of BTK inhibitors
- Zanubrutinib demonstrated sustained PFS benefit over ibrutinib in patients with R/R CLL/SLL with a median follow-up of 39 months
  - Durable PFS benefits were seen across major subgroups, including the del(17p)/*TP53*^{mut} population
  - PFS benefit was consistent across multiple sensitivity analyses, demonstrating that the PFS advantage with zanubrutinib was primarily driven by efficacy and not by tolerability
- While responses deepened over time in both arms, the objective response rate was higher with zanubrutinib, with increased rates of CR/CRi compared with ibrutinib
- Zanubrutinib continues to demonstrate a more favorable safety and tolerability profile compared with ibrutinib
- **With over 3 years of follow-up, these data reconfirm that zanubrutinib has improved efficacy over ibrutinib and a more favorable safety profile in patients with R/R CLL/SLL**

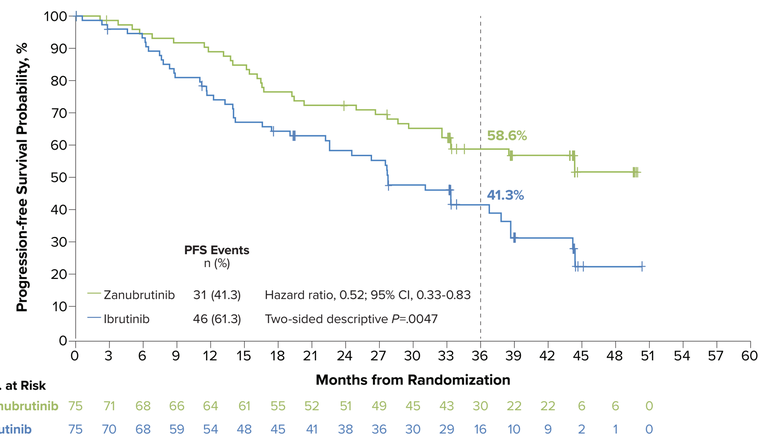
- At extended follow-up (median, 39.0 months), the PFS benefit with zanubrutinib over ibrutinib was sustained (**Figure 3**)
- PFS improvement was sustained across all major subgroups, including in high-risk patients with del(17p)/*TP53*^{mut} (**Figure 4**)

Figure 3. PFS at Extended Follow-Up



PFS, progression-free survival.

Figure 4. PFS in Patients With del(17p)/*TP53*^{mut}



PFS, progression-free survival; *TP53*, tumor protein p53.

- PFS benefit was consistent across multiple sensitivity analyses (**Table 2**)

Table 2. PFS Sensitivity Analyses

Sensitivity Analysis	Zanubrutinib n (%)	Ibrutinib n (%)	HR (95% CI)	2-sided *P*-value
Accounting only for PD and death events that occurred during active treatment	76 (23.2)	85 (26.2)	0.69 (0.50, 0.95)	.0206
Censoring for new CLL/SLL therapies	129 (39.4)	157 (48.3)	0.68 (0.54, 0.86)	.0014
Censoring for death due to COVID-19	115 (35.2)	142 (43.7	0.66 (0.52, 0.85)	.0013

CLL/SLL, chronic lymphocytic leukemia or small lymphocytic lymphoma; PD, progressive disease.

- At 36 months, overall survival was not statistically different between zanubrutinib (82.5%) and ibrutinib (79.6%) groups (HR, 0.75; 95% CI, 0.54-1.05; *P*=.0098)

Safety and Tolerability

- At median follow-up of 39 months, the safety profile of zanubrutinib remained favorable vs ibrutinib (**Table 3**)

Table 3. Adverse Events of Special Interest[a] Occurring in ≥2 Patients

	Zanubrutinib (n=324)		Ibrutinib (n=324)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infection	264 (81.5)	115 (35.5)	260 (80.2)	111 (34.3)
Opportunistic Infections	8 (2.5)	6 (1.9)	13 (4.0)	5 (1.5)
COVID-19 Related[b]	**145 (44.8)**	**56 (17.3)**	**105 (32.4)**	**38 (11.7)**
Bleeding	142 (43.8)	12 (3.7)	144 (44.4)	13 (4.0)
Major Hemorrhage	13 (4.0)	12 (3.7)	16 (4.9)	13 (4.0)
Hypertension	**86 (26.5)**	**53 (16.4)**	**80 (24.7)**	**47 (14.5)**
Atrial fibrillation/flutter	**22 (6.8)**	**10 (3.1)**	**53 (16.4)**	**16 (4.9)**
Anemia	53 (16.4)	7 (2.2)	59 (18.2)	11 (3.4)
Neutropenia	**100 (30.9)**	**72 (22.2)**	**94 (29.0)**	**72 (22.2)**
Thrombocytopenia	43 (13.3)	12 (3.7)	53 (16.4)	19 (5.9)
Second primary malignancies	46 (14.2)	26 (8.0)	52 (16.0)	19 (5.9)

[a] Pooled MedDRA preferred terms.
[b] Includes preferred terms of COVID-19, COVID-19 pneumonia, and suspected COVID-19.

- Compared with ibrutinib, zanubrutinib had lower rates of grade ≥3 and serious adverse events (AEs) and fewer AEs leading to treatment discontinuation, hospitalization, or dose reduction (**Table 4**)

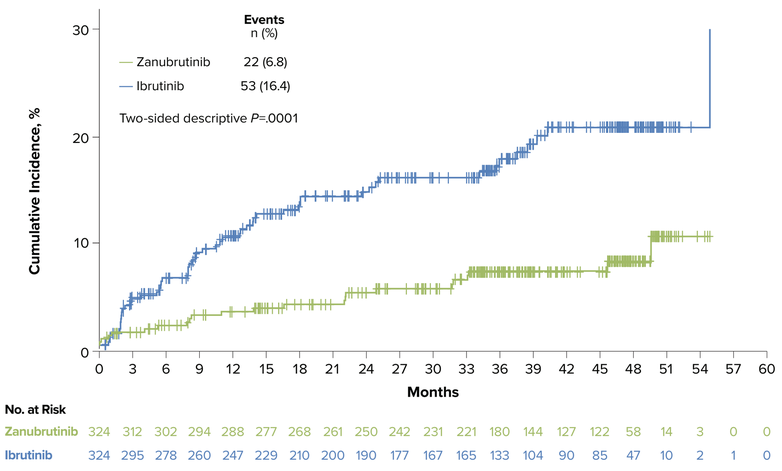
Table 4. Safety Summary

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Treatment duration, median (range), months	38.3 (0.4-54.9)	35.0 (0.1-58.4)
Any-grade adverse events, n (%)	320 (98.8)	323 (99.7)
Grade 3-5	235 (72.5)	251 (77.5)
Grade 5	41 (12.7)	40 (12.3)
Serious adverse events, n (%)	165 (50.9)	191 (59.0)
Adverse events leading to, n (%)		
Dose reduction	47 (14.5)	59 (18.2)
Dose interruption	196 (60.5)	201 (62.0)
Treatment discontinuation	64 (19.8)	85 (26.2)
Hospitalization	150 (46.3)	180 (55.6)
Cardiac adverse events, n (%)	80 (24.7)	112 (34.6)
Serious cardiac adverse events, n (%)	11 (3.4)	31 (9.6)
Cardiac adverse events leading to treatment discontinuation, n (%)	3 (0.9)	15 (4.6)
Ventricular extrasystole	1 (0.3)	0
Atrial fibrillation/flutter	1 (0.3)	6 (1.9)
Cardiac failure	1 (0.3)	2 (0.6)
Cardiac arrest	0	2 (0.6)[a]
Cardiac failure acute	0	1 (0.3)[a]
Congestive cardiomyopathy	0	1 (0.3)[a]
Myocardial infarction	0	1 (0.3)[a]
Palpitations	0	1 (0.3)
Ventricular fibrillation	0	1 (0.3)

[a] Fatal cardiac event (n=6); 1 death (myocardial infarction with ibrutinib) was not listed due to discontinuation due to diarrhea 14 days prior to the fatal event.

- Zanubrutinib continues to demonstrate a more favorable cardiac safety profile than ibrutinib, with lower rates of cardiac AEs, serious cardiac AEs, and cardiac AEs leading to treatment discontinuation
  - Despite similar hypertension AE rates, mean change from baseline in systolic blood pressure was consistently lower with zanubrutinib compared with ibrutinib; changes in diastolic blood pressure were less than systolic blood pressure across treatments
- No fatal cardiac events occurred with zanubrutinib treatment, and 6 (1.9%) fatal cardiac events occurred with ibrutinib
- Significantly fewer atrial fibrillation/flutter events occurred with zanubrutinib than with ibrutinib (**Figure 5**)

Figure 5. Time to Atrial Fibrillation/Flutter Events



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ACKNOWLEDGMENTS

The authors would like to thank the investigators, site support staff, and especially the patients and their caregivers for participating in the ALPINE study. Original slides were developed under the direction of the authors, provided by Regina Switzer, PhD, Yin Lin, PhD, Nathan McCance, BFA, and Elizabeth Hermans, PhD

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Presented at the 44th SFH Annual Meeting; March 27-29, 2024; Paris, France.
Data originally presented at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023, San Diego, CA. Abstract 3279