Final Independent Review Data Supports Sustained Benefit of Zanubrutinib Over Ibrutinib in Patients With R/R CLL/SLL in ALPINE

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CONCLUSIONS

- ALPINE is the first study to demonstrate PFS superiority in a global head-to-head comparison of BTK inhibitors
- At a median follow-up of 3.5 years of IRC data, the study showed consistent PFS benefits of zanubrutinib over ibrutinib
- IRC efficacy results have a high concordance rate with previously published INV results, consolidating the superiority of zanubrutinib over ibrutinib in patients with R/R CLL/SLL by INV, including in patients with del(17p)/*TP53* mutation, with an improved tolerability and safety profile compared with ibrutinib[4,5]

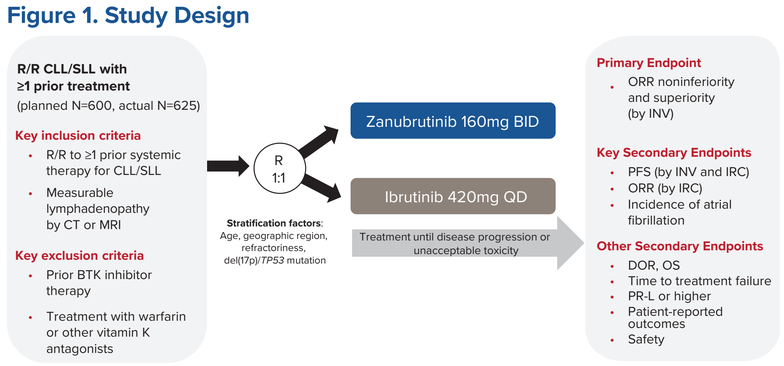
INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibitors are a treatment option for patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), offering improved outcomes compared with chemotherapy-based regimens[1]
- Zanubrutinib is a next-generation BTK inhibitor and has been designed for increased potency, greater BTK specificity, and exposure coverage above half-maximal inhibitory concentration during the dosing interval to improve efficacy and tolerability[2]
- ALPINE (NCT03734016) was a phase 3, randomized, global study in patients with relapsed or refractory (R/R) CLL/SLL[3,4]
  - Final results (data cutoff: Feb 28, 2024), including efficacy based on investigator assessment (INV), have been published[5]
  - At an overall median follow-up of 42.5 months, the progression-free survival (PFS) benefit with zanubrutinib vs ibrutinib was sustained
  - Durable PFS benefits were seen across major subgroups, including the del(17p)/*TP53* mutation population
- Here, we report final efficacy results (data cutoff: Feb 28, 2024) based on independent review committee assessment (IRC)

METHODS

- Study design and methods have been previously published[3,4] and are summarized in **Figure 1**

Figure 1. Study Design



Data cutoff: Feb 28, 2024.
Abbreviations: BID, twice daily; BTK, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; CT, computed tomography; DOR, duration of response; INV, investigator assessed; IRC, independent review committee assessed; MRI, magnetic resonance imaging; ORR, overall response rate; OS, overall survival; PR, partial response; PR-L, partial response with lymphocytosis; QD, once daily; R, randomization; R/R, relapsed or refractory; SLL, small lymphocytic lymphoma.

Study assessments

- The overall response rate (ORR) (partial response [PR] or higher, defined as complete response [CR]/complete response with incomplete hematopoietic recovery [CRi] + nodular PR + PR) was determined by INV using the 2008 International Workshop on CLL guidelines[6] with modification for treatment-related lymphocytosis[7] in patients with CLL and per Lugano classification for non-Hodgkin lymphoma in patients with SLL[8]

RESULTS

Disposition and baseline characteristics

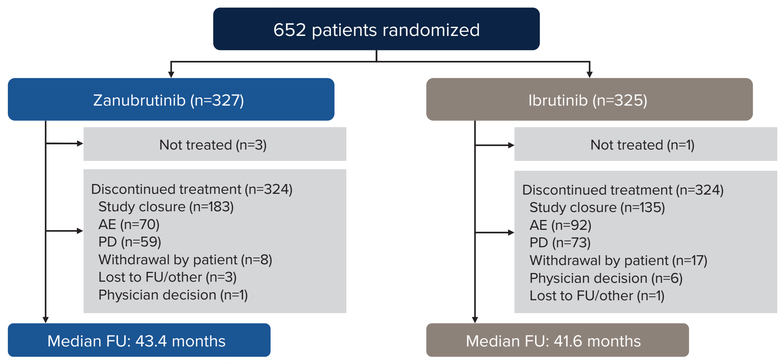
- In ALPINE, 652 patients were randomized to receive zanubrutinib (n=327) or ibrutinib (n=325) (**Table 1** and **Figure 2**)
- As of study closure (Feb 28, 2024), 183 of 327 patients (56.0%) and 135 of 325 patients (41.5%) were receiving zanubrutinib and ibrutinib, respectively
- At a median study follow-up of 42.5 months, IRC data showed that the PFS benefit of zanubrutinib over ibrutinib was sustained (hazard ratio [HR], 0.69; 95% CI, 0.55-0.87) and consistent with INV PFS (HR, 0.68; 95% CI, 0.54-0.84) (**Figure 3**)

Table 1. Demographics, Disease History, and Characteristics

	Zanubrutinib (n=327)	Ibrutinib (n=325)
Age, median (range), years	67 (35-90)	68 (35-89)
Male	213 (65.1)	232 (71.4)
ECOG PS ≥1, n (%)	198 (60.6)	203 (62.5)
Race, n (%)		
White	261 (79.8)	265 (81.5)
Asian	47 (14.4)	44 (13.5)
Black or African American	4 (1.2)	2 (0.6)
Native Hawaiian or other Pacific Islander	3 (0.9)	0
Multiple	1 (0.3)	0
Other/not reported/unknown	11 (3.4)	14 (4.3)
Prior 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)
Missing	7 (2.1)	14 (4.3)
Complex karyotype (≥3 abnormalities)[a]		
Yes	56 (17.1)	70 (21.5)
No	153 (46.8)	130 (40.0)
Missing	118 (36.1)	125 (38.5)
Complex karyotype (≥5 abnormalities)[a]		
Yes	32 (9.8)	38 (11.7)
No	177 (54.1)	162 (49.8)
Missing	118 (36.1)	125 (38.5)
Bulky disease (≥5 cm), n (%)	145 (44.3)	149 (45.8)

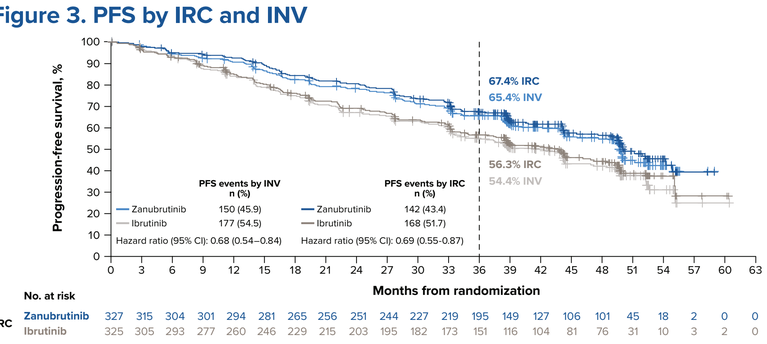
[a]Centrally assessed.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy-chain variable.

Figure 2. Study Flow Diagram



Abbreviations: AE, adverse event, FU, follow-up; PD, progressive disease.

Figure 3. PFS by IRC and INV

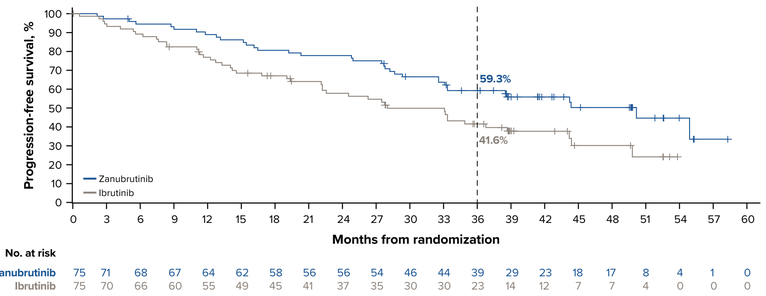


No. at risk																					
IRC	Zanubrutinib	327	315	304	301	294	281	265	256	251	244	227	219	195	149	127	106	101	45	18	2	0	0
	Ibrutinib	325	305	293	277	260	246	229	215	203	195	182	173	151	116	104	81	76	31	10	3	2	0
INV	Zanubrutinib	327	315	302	295	287	272	258	247	242	236	218	210	189	151	128	109	104	43	19	2	0	0
	Ibrutinib	325	305	293	273	258	242	229	212	200	194	183	173	148	116	101	77	74	30	10	2	1	0

Abbreviations: INV, investigator assessment; IRC, independent review committee assessment; PFS, progression-free survival.

- Benefits in PFS with zanubrutinib based on IRC were also observed across major subgroups, including in patients with del(17p)/*TP53* mutation (HR, 0.56; 95% CI, 0.36-0.88) (**Figures 4** and **5**)

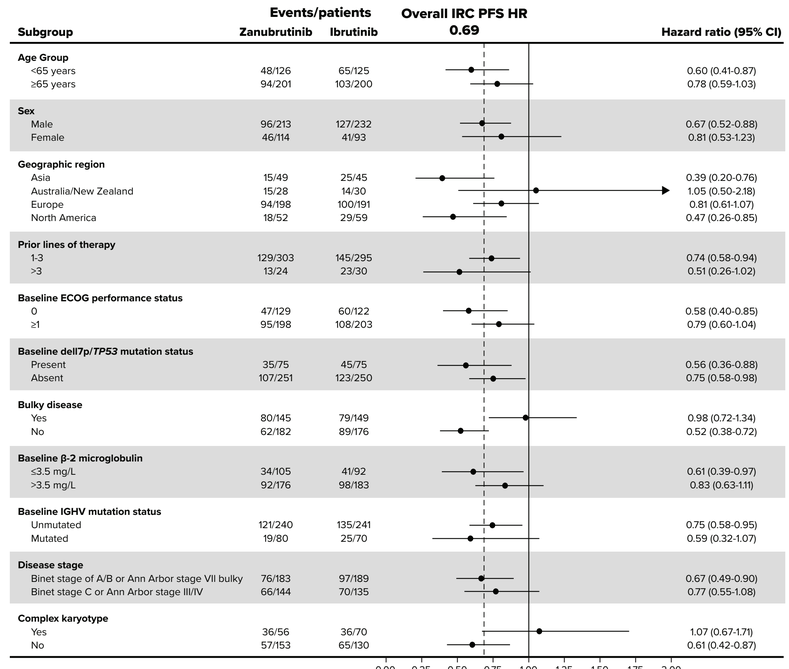
Figure 4. PFS by IRC (del[17p] and/or *TP53*mut population)



No. at risk																				
Zanubrutinib	75	71	68	67	64	62	58	56	56	54	46	44	39	29	23	18	17	8	4	1	0
Ibrutinib	75	70	66	60	55	49	45	41	37	35	30	30	23	14	12	7	7	4	0	0	0

Abbreviations: IRC, independent review committee assessment; mut, mutation; PFS, progression-free survival.

Figure 5. Subgroup Analysis



Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IGHV, immunoglobulin heavy-chain variable; IRC, independent review committee assessment; PFS, progression-free survival.

- ORR by IRC (defined as PR or better) remained higher with zanubrutinib vs ibrutinib (88.4% vs 76.6%), with a response ratio of 1.15 (95% CI, 1.07-1.23); the rates of partial response with lymphocytosis or better, were 91.4% vs 83.1%, respectively (**Table 2**)
- CR/CRi rates of 13.5% with zanubrutinib and 8.6% with ibrutinib were observed

Table 2. ORR Comparison: INV vs IRC

	INV[7]		IRC	
Best overall response, n (%)	**Zanubrutinib (n=327)**	**Ibrutinib (n=325)**	**Zanubrutinib (n=327)**	**Ibrutinib (n=325)**
CR	37 (11.3)	22 (6.8)	44 (13.5)	25 (7.7)
CRi	1 (0.3)	3 (0.9)	0	3 (0.9)
nPR	7 (2.1)	0	4 (1.2)	1 (0.3)
PR	235 (71.9)	220 (67.7)	241 (73.7)	220 (67.7)
PR-L	15 (4.6)	24 (7.4)	10 (3.1)	21 (6.5)
SD	21 (6.4)	36 (11.1)	15 (4.6)	34 (10.5)
PD	2 (0.6)	6 (1.8)	3 (0.9)	7 (2.2)
Non-PD	N/A	N/A	2 (0.6)	0
Discontinued prior to first assessment	9 (2.8)	14 (4.3)	8 (2.4)	12 (3.7)
Not evaluable/not assessed	0	0	0	2 (0.6)
ORR (PR or higher), n (%) (95% CI)	280 (85.6) (81.3-89.2)	245 (75.4) (70.3-80.0)	289 (88.4) (84.4-91.6)	249 (76.6) (71.6-81.1)
Response ratio (95% CI)	1.13 (1.05-1.22)		1.15 (1.07-1.23)	
CR/CRi, n (%) (95% CI)	38 (11.6) (8.4-15.6)	25 (7.7) (5.0-11.1)	44 (13.5) (9.9-17.6)	28 (8.6) (5.8-12.2)
Rate of PR-L or higher, n (%) (95% CI)	295 (90.2) (86.5-93.2)	269 (82.8) (78.2-86.7)	299 (91.4) (87.9-94.2)	270 (83.1) (78.5-87.0)

Abbreviations: CR, complete response; CRi, complete response with incomplete hematopoietic recovery; INV, investigator assessment; IRC, independent review committee assessment; N/A, not available; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

- PFS by INV vs IRC (76.8% with zanubrutinib and 73.8% with ibrutinib) and overall responses (95.4% and 93.8%, respectively) had high concordance rates (**Table 3**)

Table 3. INV and IRC Data Concordance

Concordance rate between INV and IRC, %	Zanubrutinib	Ibrutinib
Concordance rate for PFS[a]	76.8	73.8
Concordance rate for ORR (PR or higher)	95.4	93.8
Concordance rate for CR/CRi	92.7	97.2
Concordance rate for PR-L or higher	95.7	92.3

[a]Definition of concordance: IRC and INV agreed on whether progressive disease occurred; if progressive disease did occur, the timing differed by <1 month.
Abbreviations: CR, complete response; CRi, complete response with incomplete hematopoietic recovery; INV, investigator assessment; IRC, independent review committee assessment; ORR, overall response rate; PFS, progression-free survival; PR, partial response; PR-L, partial response with lymphocytosis.

Safety

- The safety results with the same data cutoff date of this study were published[5]

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DISCLOSURES

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