Zanubrutinib Demonstrates Superior Progression-Free Survival Compared With Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: Results From Final Analysis of ALPINE Randomized Phase 3 Study

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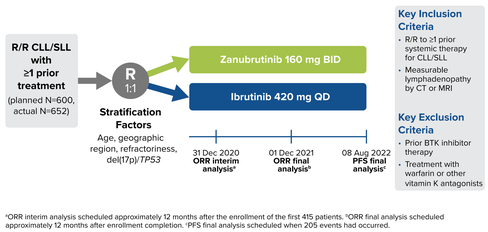
INTRODUCTION

- B-cell antigen receptor (BCR) signaling, which is dependent on Bruton tyrosine kinase (BTK), is required for tumor expansion and proliferation in CLL and B-cell lymphomas[1]
- Ibrutinib, a first-in-class, covalent BTK inhibitor, has transformed CLL therapy; however, it has properties that limit use
  - Treatment discontinuation from toxicities has been reported in 16-23% of patients[2-5]
  - Exposure coverage between dosing intervals falls below IC_{wt}, and variable BTK occupancy at trough has been observed[6]
- Zanubrutinib is a second-generation BTK inhibitor that was specifically designed to improve BTK specificity over ibrutinib
  - Zanubrutinib has exposure coverage above its IC_{50}[7]
  - Higher drug concentration/IC_{50} ratios would be expected to lead to more sustained and complete BTK inhibition to improve efficacy
- In a global, randomized phase 3 study (ALPINE; NCT03734016), zanubrutinib was compared head to head with ibrutinib in patients with relapsed or refractory (R/R) CLL/SLL[8,10]
- At a predefined response analysis in the ALPINE study, zanubrutinib demonstrated superior overall response rate (ORR) compared with ibrutinib by IRC and investigator (INV)[9,10]
- This presentation reports the clinical outcomes of the final PFS analysis of the ALPINE study

METHODS

- The ALPINE study was designed to compare the efficacy, safety, and adverse event (AE) profile of zanubrutinib with those of ibrutinib in patients with R/R CLL/SLL (**Figure 1**); complete methodology is available in Hillmen et al 2023[8] and Brown et al 2023[10]
- As the primary endpoint of ORR was superior with zanubrutinib in preplanned analyses,[9,10] the key secondary efficacy endpoint of PFS was tested for noninferiority under hierarchical testing in this PFS analysis when 205 events had occurred
  - If PFS noninferiority between zanubrutinib and ibrutinib was demonstrated, superiority of zanubrutinib vs ibrutinib would be tested and claimed if the 2-sided *P* value was <0.04996

Figure 1. ALPINE Study Design



[a]ORR interim analysis scheduled approximately 12 months after the enrollment of the first 415 patients. [b]ORR final analysis scheduled approximately 12 months after enrollment completion. [c]PFS final analysis scheduled when 205 events had occurred.

RESULTS

- A total of 652 patients from 15 countries were randomized to receive zanubrutinib (n=327) or ibrutinib (n=325)
- At the time of data cutoff (8 August 2022), 72.8% and 58.5% of patients were still receiving zanubrutinib or ibrutinib, respectively
  - The most common reasons for treatment discontinuation were AEs (16.2% vs 22.8%) or progressive disease (7.3% vs 12.9%) with zanubrutinib vs ibrutinib, respectively
- Demographic and clinical characteristics of the 2 groups were generally balanced at baseline (**Table 1**)

RESULTS (cont.)

Table 1. Patient Demographics and Disease Characteristics

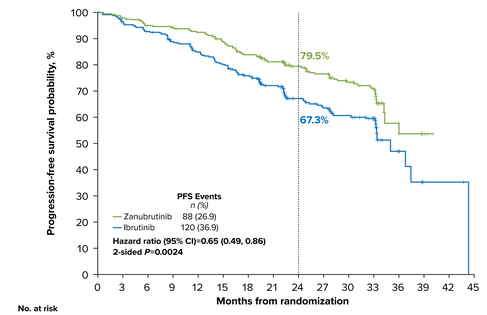
Characteristics	Zanubrutinib (n=327)	Ibrutinib (n=325)
Median age (range), years	**67 (35-90)**	**68 (35-89)**
Aged ≥65 years, n (%)	201 (61.5)	200 (61.5)
Male, n (%)	**213 (65.1)**	**232 (71.4)**
ECOG PS ≥1, n (%)	**198 (60.6)**	**203 (62.5)**
Median prior lines of systemic therapy (range)	**1 (1-6)**	**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)
del(11q), n (%)	**91 (27.8)**	**88 (27.1)**
IGHV mutational status, n (%)		
Mutated	79 (24.2)	70 (21.5)
Unmutated	239 (73.1)	239 (73.5)
Complex karyotype[a]	**56 (17.1)**	**70 (21.5)**

[a]Complex karyotype is defined as having ≥3 abnormalities.

Efficacy

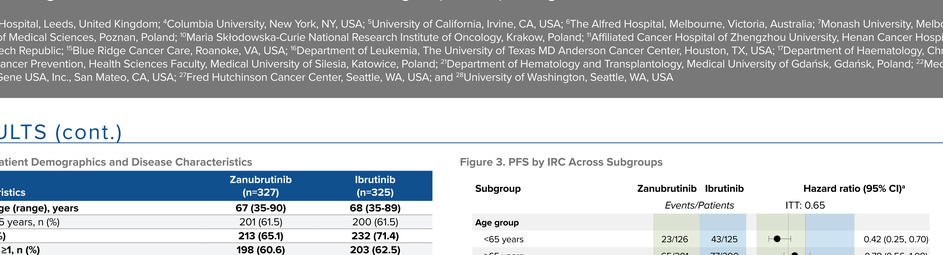
- With a median follow-up of 29.6 month, zanubrutinib PFS by IRC was superior to ibrutinib in the ITT population; identical statistical values were reported when assessed by INV (**Figure 2**)
  - Median PFS by IRC was 35.0 month (95% CI: 33.2, 44.3) with ibrutinib but not reached with zanubrutinib
- PFS favored zanubrutinib across major subgroups (**Figure 3**), including patients with del(17p)/*TP53*[mut] (**Figure 4**)
- Zanubrutinib ORRs were higher than those of ibrutinib, with 86% vs 76% (nominal *P*=0.0007) by IRC and 83.5% vs 74.2% (nominal *P*=0.0035) by INV
- As of 8 August 2022, fewer deaths were reported in the zanubrutinib group than in the ibrutinib group
  - Median overall survival was not reached in either treatment group

Figure 2. PFS by IRC in All Patients



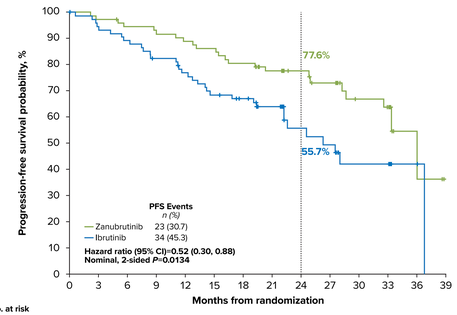
No. at risk																
Zanubrutinib	327	315	304	301	294	280	263	226	172	161	125	113	14	2	0	
Ibrutinib	325	305	293	277	260	246	228	191	133	123	98	87	9	2	2	0

Figure 3. PFS by IRC Across Subgroups



[a]Hazard ratio and 95% CI were unstratified for subgroups.

Figure 4. PFS by IRC in Patients With del(17p)/*TP53*[mut]



No. at risk														
Zanubrutinib	75	71	68	67	64	62	58	49	35	30	21	19	3	0
Ibrutinib	75	70	66	60	55	49	45	34	18	16	10	10	2	0

Safety

- Zanubrutinib safety profile was favorable to that of ibrutinib (**Table 2**)
- The most common AEs occurring in ≥20% of patients in either arm were diarrhea (16% vs 24%), hypertension (22% vs 20%), neutropenia (23% vs 18%), COVID-19 (23% vs 18%), and upper respiratory tract infection (21% vs 14%) with zanubrutinib vs ibrutinib, respectively
- The rate of atrial fibrillation/flutter was lower with zanubrutinib compared with ibrutinib (5.2% vs 13.3%; **Figure 5**)
- Six (1.9%) serious cardiac AEs were reported with zanubrutinib (atrial fibrillation/flutter, n=2; myocardial infarction/acute coronary syndrome, n=2; congestive heart failure, n=2) vs 25 (7.7%) with ibrutinib (**Table 3**)
- There were no fatal cardiac events with zanubrutinib vs 6 (1.9%) with ibrutinib

Table 2. Overall Safety Profiles

Safety profile, n (%)	Zanubrutinib (n=324)	Ibrutinib (n=324)
Median treatment duration, months	**28.4**	**24.3**
AE (any grade)	**318 (98.1)**	**321 (99.1)**
Grades 3 to 5	218 (67.3)	228 (70.4)
Grade 5	33 (10.2)	36 (11.1)
Serious AE	**136 (42.0)**	**162 (50.0)**
AEs leading to		
Dose reduction	40 (12.3)	55 (17.0)
Dose interruption	162 (50.0)	184 (56.8)
Treatment discontinuation	50 (15.4)	72 (22.2)

Table 3. Cardiac Profiles and Adverse Events

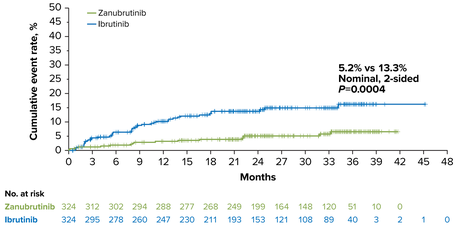
Cardiac AEs, n (%)	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac AEs	**69 (21.3)**	**96 (29.6)**
Serious cardiac AEs	**6 (1.9)**	**25 (7.7)**
Cardiac AEs leading to treatment discontinuation	**1 (0.3)**	**14 (4.3)**
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation	0	5 (1.5)
Cardiac arrest	0	2 (0.6)[a]
Cardiac failure	0	2 (0.6)
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]Cardiac deaths. One death not listed due to myocardial infarction with ibrutinib discontinuation due to diarrhea 14 days before the fatal event.

CONCLUSIONS

- Zanubrutinib demonstrated superior PFS over ibrutinib in patients with R/R CLL/SLL
  - PFS benefit seen across all major subgroups, including the del(17p)/*TP53*[mut] population
- Zanubrutinib had a favorable safety profile compared with that of ibrutinib
  - Zanubrutinib had a lower rate of grade ≥3 and serious AEs as well as fewer AEs leading to treatment discontinuation and dose reduction
  - Zanubrutinib had a better cardiac profile than ibrutinib, with lower rates of atrial fibrillation, serious cardiac events, cardiac events leading to treatment discontinuation, and no fatal cardiac events vs 1.9% with ibrutinib
- ALPINE is the first study to demonstrate PFS superiority in a head-to-head comparison of BTK inhibitors in patients with R/R CLL/SLL
- Zanubrutinib has now proven superiority to ibrutinib in both PFS and ORR in R/R CLL/SLL

Figure 5. Atrial Fibrillation/Flutter Events



No. at risk																
Zanubrutinib	324	312	302	294	288	277	268	249	199	164	148	120	51	10	0	
Ibrutinib	324	295	278	260	247	230	211	193	153	121	108	89	40	3	2	1	0

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DISCLOSURES

Disclosures are listed in Brown et al 2023, accessible through the Quick Response (QR) Code.

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Plain language summary

The ALPINE final analysis manuscript (Brown et al N Engl J Med 2023) and plain language summary can be accessed through the Quick Response (QR) Codes.

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