Poster 264

Zanubrutinib Demonstrates Superior Progression-Free Survival (PFS) vs Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (R/R CLL/SLL): Final PFS Analysis of Randomized Phase 3 ALPINE Study

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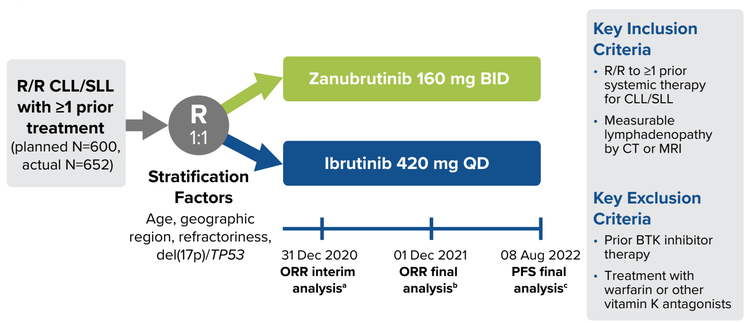
INTRODUCTION

- B-cell antigen receptor (BCR) signaling, which is dependent on Bruton tyrosine kinase (BTK), is required for tumor expansion and proliferation in chronic lymphocytic leukemia (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_{50}, 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/small lymphocytic lymphoma (SLL)[8-10]
- At a predefined response analysis in the ALPINE study, zanubrutinib demonstrated superior overall response rate (ORR) compared with ibrutinib by independent review committee (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[9] 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 <.04996

Figure 1. ALPINE Study Design[9,10]



[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**)

Table 1. Patient Demographics and Disease Characteristics[10]

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 lines of systemic therapy, median (range), n	**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 months, PFS with zanubrutinib by IRC was superior to that with ibrutinib in the ITT population; identical statistical values were reported when assessed by INV (**Figure 2**)
  - Median PFS by IRC was 35.0 months (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*=.0007) by IRC and 83.5% vs 74.2% (nominal *P*=.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[10]

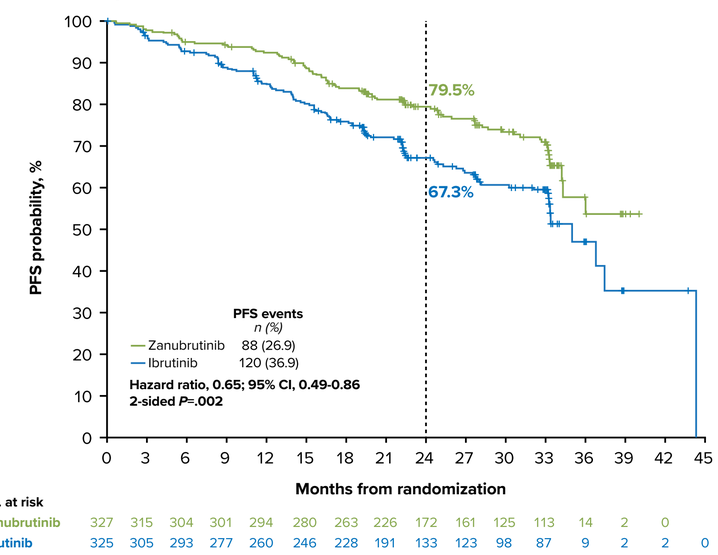
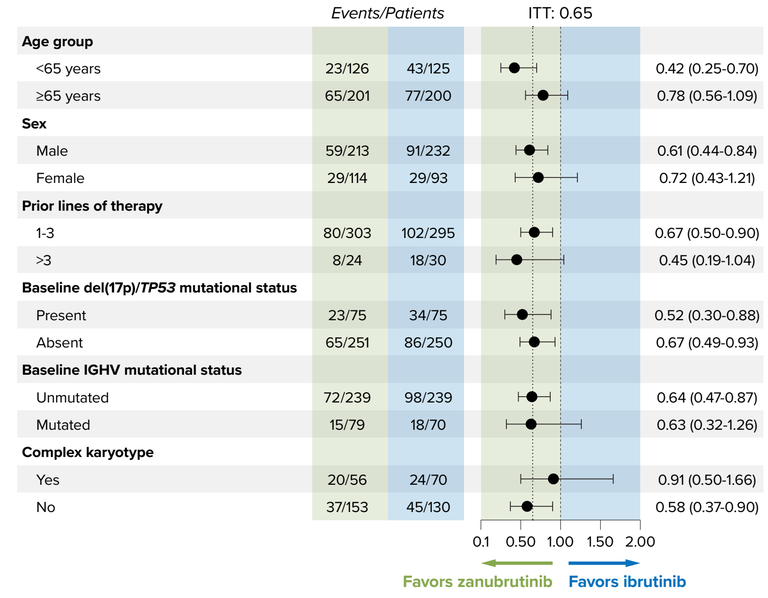
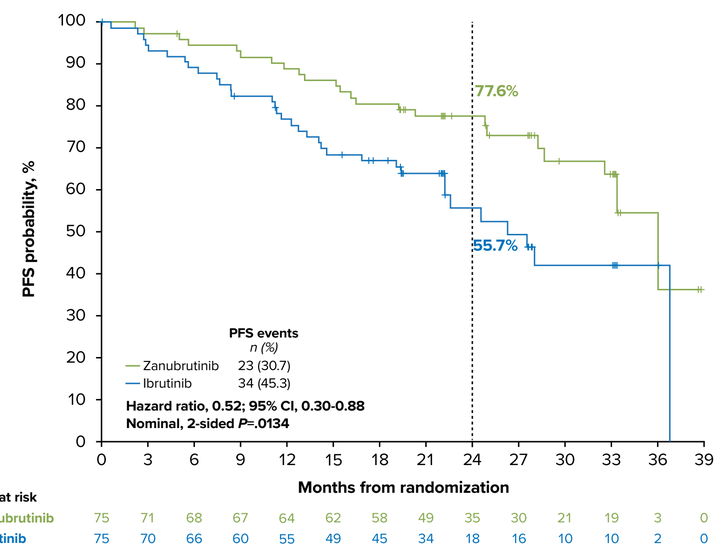


Figure 3. PFS by IRC Across Subgroups[10]



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

Figure 4. PFS in Patients With del(17p)/*TP53*[mut] by IRC[10]



Safety

- The 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**)
- Serious cardiac AEs were reported in 6 patients (1.9%) in the zanubrutinib arm (atrial fibrillation/flutter, n=2; myocardial infarction/acute coronary syndrome, n=2; congestive heart failure, n=2) vs 25 (7.7%) in the ibrutinib arm (**Table 3**)
- There were no fatal cardiac events with zanubrutinib vs 6 (1.9%) with ibrutinib

CONCLUSIONS

- Zanubrutinib demonstrated superior PFS over ibrutinib in patients with R/R CLL/SLL
  - PFS benefit was 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 toxicity profile than ibrutinib, with lower rates of atrial fibrillation, serious cardiac events, cardiac events leading to treatment discontinuation, and no fatal cardiac events vs 6 fatal cardiac events in patients treated 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

Table 2. Overall Safety Profiles[10]

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Median treatment duration, months	**28.4**	**24.3**
AEs (any grade), n (%)	**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 AEs, n (%)	**136 (42.0)**	**162 (50.0)**
AEs leading to, n (%)		
Dose reduction	40 (12.3)	55 (17.0)
Dose interruption	162 (50.0)	184 (56.8)
Treatment discontinuation	50 (15.4)	72 (22.2)

Figure 5. Atrial Fibrillation/Flutter Events[10]

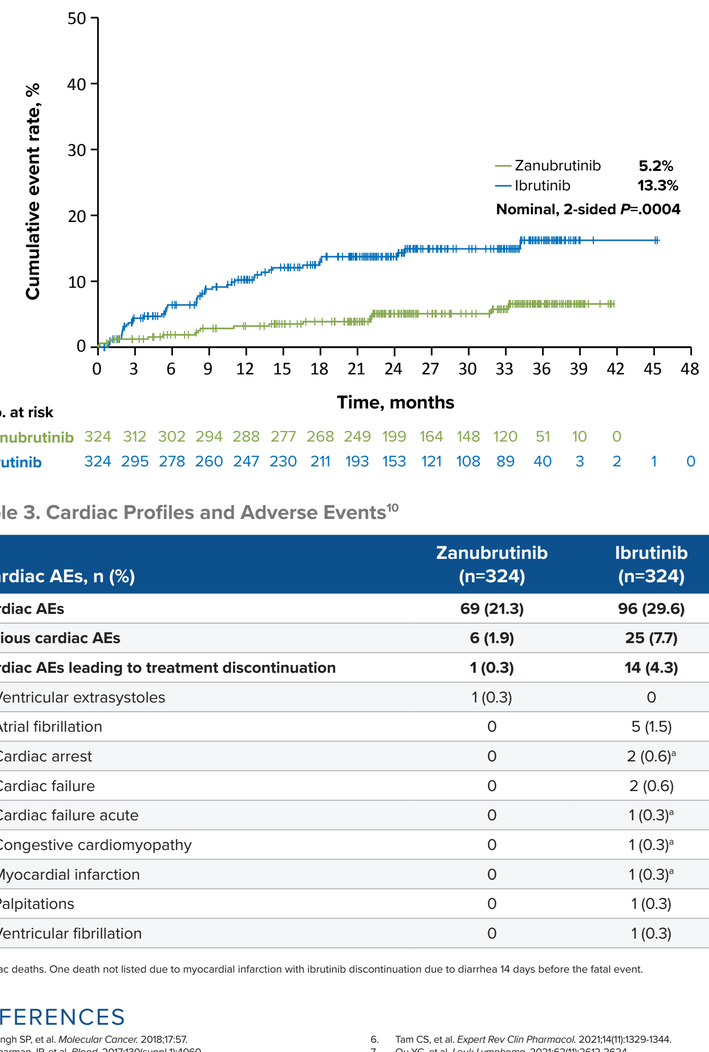


Table 3. Cardiac Profiles and Adverse Events[10]

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.

REFERENCES

1. Singh SP, et al. *Molecular Cancer.* 2018;17:57.
2. Sharman JP, et al. *Blood.* 2017;130(suppl 1):4060.
3. Mato AR, et al. *Haematologica.* 2018;103(5):874-879.
4. Munir T, et al. *Am J Hematol.* 2019;94(12):1353-1363.
5. Ghia P, et al. EHA 2021. Abstract EP636.
6. Tam CS, et al. *Expert Rev Clin Pharmacol.* 2021;14(11):1329-1344.
7. Ou YC, et al. *Leuk Lymphoma.* 2021;62(11):2612-2624.
8. Hillmen P, et al. *Future Oncol.* 2020;16(10):517-523.
9. Hillmen P, et al. *J Clin Oncol.* 2023;41(5):1035-1045.
10. Brown JR, et al. *N Engl J Med.* 2023;388(4):319-332.

DISCLOSURES

Disclosures are listed in Brown et al 2023,[10] accessible through the Quick Response (QR) code below.

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