First Interim Analysis of ALPINE Study: Results of a Phase 3 Randomized Study of Zanubrutinib vs Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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INTRODUCTION

- Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are progressive B-cell malignancies that are characterized by progressive accumulation of leukemic cells in the peripheral blood, bone marrow, and lymphoid tissue[1]
  - Despite standard treatment with chemoimmunotherapy, the clinical course of CLL is usually characterized by consecutive episodes of disease progression and renewed need for therapy[2]
  - Patients with del(17p) and TP53 mutations tend to have poorer outcomes, and respond poorly to chemoimmunotherapy[3]
- In recent years, treatment of CLL/SLL has been transformed with the advent of effective inhibitors of B-cell receptor signaling, such as the Bruton tyrosine kinase (BTK) inhibitor, ibrutinib[4]
  - Ibrutinib has well-described off-target effects that contribute to its toxicity profile, notably an increased risk for cardiovascular disease, including atrial fibrillation, hypertension, and hemorrhage[5]
  - Cardiovascular AEs, diarrhea, and rash observed in patients treated with ibrutinib have been associated with off-target inhibition of kinases such as EGFR, HER, and TEC[5]
- Zanubrutinib is an irreversible, potent, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases[6,7]
  - Efficacy and safety of zanubrutinib has been recently demonstrated in two large, randomized studies in Waldenström macroglobulinemia and relapsed/refractory CLL/SLL, with lower rates of atrial fibrillation when compared to ibrutinib[8,9]
  - Preliminary data showing high response rates with zanubrutinib in untreated patients with the high-risk genomic abnormality, del(17p), have been recently published[10,11]
- Here, we present results from the preplanned interim analysis of ALPINE, a phase 3 trial of zanubrutinib versus ibrutinib in CLL/SLL

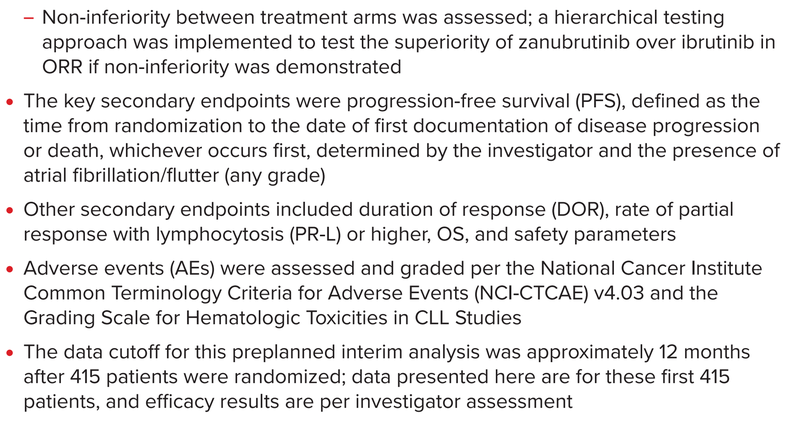
METHODS

- ALPINE (BGB-3111-305; NCT03734016) is an international, randomized, open-label, phase 3 study comparing zanubrutinib versus ibrutinib in patients with relapsed/refractory (R/R) CLL/SLL
- Eligible patients were ≥18 years of age, had CLL/SLL that was R/R to ≥1 prior systemic therapy, had measurable lymphadenopathy by computed tomography (CT) or magnetic resonance imaging (MRI) scan, and had Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.
  - Refractory disease was defined as either no objective response or disease progression within 6 months of the last CLL/SLL treatment, and relapsed disease was defined as patients whose disease relapses more than 6 months after the last CLL/SLL treatment and subsequently progressed
- Patients with current or past Richter's transformation, prior BTK inhibitor therapy, or treatment with warfarin or other vitamin K antagonists were excluded from the study
- Study patients were randomly assigned 1:1 to receive zanubrutinib 160 mg twice daily or ibrutinib 420 mg once daily until disease progression or withdrawal of consent
- Randomization was stratified by age (<65 years vs ≥65 years), geographic region (China versus non-China), refractory status (yes or no), and del(17p)/TP53 mutation status (present or absent)
- The primary endpoint was overall response rate (ORR) as determined by investigator assessment using the 2008 International Workshop on CLL guidelines and the Lugano criteria for SLL
  - ORR included complete response (CR), complete response with incomplete bone marrow recovery (CRi), nodular PR, or PR and was assessed locally by the investigator
  - Non-inferiority between treatment arms was assessed; a hierarchical testing approach was implemented to test the superiority of zanubrutinib over ibrutinib in ORR if non-inferiority was demonstrated
- The key secondary endpoints were progression-free survival (PFS), defined as the time from randomization to the date of first documentation of disease progression or death, whichever occurs first, determined by the investigator and the presence of atrial fibrillation/flutter (any grade)
- Other secondary endpoints included duration of response (DOR), rate of partial response with lymphocytosis (PR-L) or higher, OS, and safety parameters
- Adverse events (AEs) were assessed and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03 and the Grading Scale for Hematologic Toxicities in CLL Studies
- The data cutoff for this preplanned interim analysis was approximately 12 months after 415 patients were randomized; data presented here are for these first 415 patients, and efficacy results are per investigator assessment

RESULTS

- Between November 5, 2018 and December 20, 2019, 415 patients were randomized into the study; 204/207 patients in the zanubrutinib arm and 207/208 patients in the ibrutinib arm received their assigned treatment (**Figure 1**)
- With a median follow-up of 15.3 months in the zanubrutinib arm and 15.4 months in the ibrutinib arm, 87.4% of the zanubrutinib arm and 75.5% of the ibrutinib arm were still receiving treatment
- More patients discontinued treatment in the ibrutinib arm (24%) than in the zanubrutinib arm (11.1%); for the patients who went off treatment, the most common reason for discontinuation was an AE

Figure 1. Patient Disposition



AE, adverse event; PD, progressive disease.

- Treatment arms were well balanced for demographic and disease characteristics (**Table 1**)
- In the zanubrutinib arm, 62.3% of patients were age ≥65 years versus 61.5% in the ibrutinib arm, 68.6% in the zanubrutinib arm were male versus 75% in the ibrutinib arm, and 7.3% in the zanubrutinib arm had >3 prior lines of therapy versus 10.1% in the ibrutinib arm
- In the zanubrutinib arm, 11.6% had del(17p) compared with 12.5% in the ibrutinib arm

Table 1. Baseline Patient and Disease Characteristics

Characteristics	Zanubrutinib (n=207)	Ibrutinib (n=208)
Age, median (range), y	67 (35, 90)	67 (36, 89)
Age ≥65 years, n (%)	129 (62.3)	128 (61.5)
Male, n (%)	142 (68.6)	156 (75.0)
Disease stage, n (%)		
Binet stage A/B or Ann Arbor stage I/II	122 (58.9)	124 (59.6)
Binet stage C or Ann Arbor stage III/IV	85 (41.1)	84 (40.4)
ECOG performance status ≥1, n (%)	128 (61.8)	132 (63.5)
Number of prior lines of therapy, median (range)	1 (1-6)	1 (1-8)
>3 prior lines, n (%)	15 (7.3)	21 (10.1)
Prior chemoimmunotherapy, n (%)	166 (80.2)	158 (76.0)
del(17p) and/or mutant *TP53*, n (%)	41 (19.8)[a]	38 (18.3)
del(17p), n (%)	24 (11.6)	26 (12.5)
TP53 mutated, n (%)	29 (14.0)[a]	24 (11.5)
del(11q), n (%)	61 (29.5)	55 (26.4)
Bulky disease (≥ 5 cm), n (%)	106 (51.2)	105 (50.5)

[a]2 patients had missing data. ECOG, Eastern Cooperative Oncology Group.

RESULTS (CONT)

- After a median follow-up of 15 months, ORR was significantly higher with zanubrutinib (78.3%) versus ibrutinib (62.5%; 2-sided *P*=.0006, pre-specified α=.0099)
- In the subset of patients with del(17p), ORR was 83.3% for zanubrutinib versus 53.8% for ibrutinib (**Table 2**)

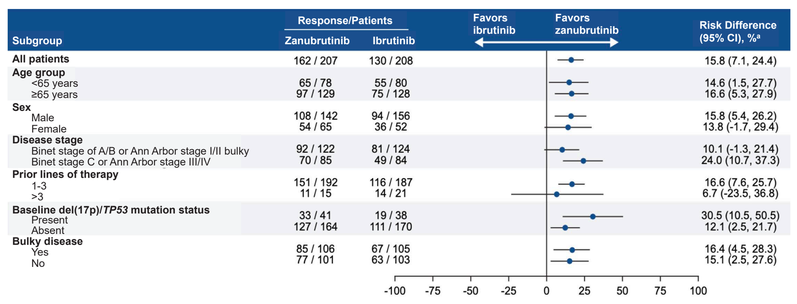
Table 2. ORR by Investigator Assessment

Parameter, n (%)	Zanubrutinib (n=207)	Ibrutinib (n=208)
Primary endpoint: ORR (PR+CR)	162 (78.3)	130 (62.5)
95% CI	72.0, 83.7[a]	55.5, 69.1[a]
CR/CRi	4 (1.9)	3 (1.4)
nPR	1 (0.5)	0
PR	157 (75.8)	127 (61.1)
ORR (PR-L+PR+CR)	183 (88.4)	169 (81.3)
PR-L	21 (10.1)	39 (18.8)
SD	17 (8.2)	28 (13.5)
PD	1 (0.5)	2 (1.0)
Discontinued or new therapy prior to 1st assessment	6 (2.9)	9 (4.3)
	del(17p) (n=24)	**del(17p) (n=26)**
ORR (PR+CR), n (%)	20 (83.3)	14 (53.8)

[a]Superiority 2-sided *P*=.0006 compared with pre-specified α=.0099. CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

- ORR favored the zanubrutinib arm compared with the ibrutinib arm in most key patient subgroups, including age, sex, disease stage, number of prior lines of therapy, mutation status, and bulky disease (**Figure 2**)

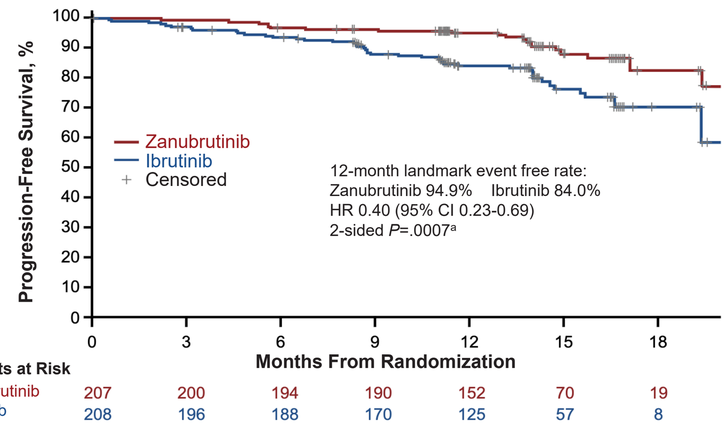
Figure 2. ORR by Investigator Assessment – Key Patient Subgroups



[a]Unstratified rate difference and 95% CI. ORR, overall response rate.

- With a median PFS follow-up time of 14 months, the investigator-assessed 12-month PFS was 94.9% for the zanubrutinib arm and 84% for the ibrutinib arm (2-sided *P*=.0007) through the cut-off date (**Figure 3**)

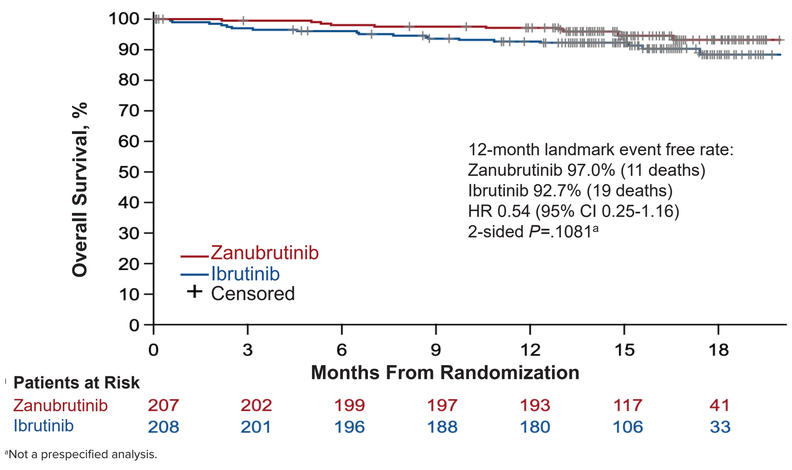
Figure 3. PFS by Investigator Assessment



[a]Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events are reached. Median PFS follow-up was 14.0 months for both zanubrutinib and ibrutinib arms by reverse KM method. PFS, progression-free survival.

- The 12-month overall survival rate was 97% in the zanubrutinib arm compared with 92.7% in the ibrutinib arm (2-sided *P*=.1081; **Figure 4**)

Figure 4. Overall Survival



[a]Not a prespecified analysis.

- Most patients experienced an AE, regardless of treatment arm (**Table 3**)
- Grade 3 or higher AEs were similar in the zanubrutinib arm versus the ibrutinib arm, while serious or fatal AEs were numerically higher in the ibrutinib versus the zanubrutinib arm
- The rate of AEs leading to discontinuation were lower with zanubrutinib; 13% of patients in the ibrutinib arm discontinued treatment due to AEs compared with 7.8% in the zanubrutinib arm, and 5.8% of patients had fatal AEs in the ibrutinib arm compared with 3.9% in the zanubrutinib arm

Table 3. Safety Summary

Parameter, n (%)	Zanubrutinib (n=204)	Ibrutinib (n=207)
Any AE	195 (95.6)	205 (99.0)
Any grade ≥3 AE	114 (55.9)	106 (51.2)
Serious AEs	56 (27.5)	67 (32.4)
Fatal AEs	8 (3.9)	12 (5.8)
AEs leading to dose reduction	23 (11.3)	25 (12.1)
AEs leading to dose interruption	81 (39.7)	84 (40.6)
AEs leading to treatment discontinuation	16 (7.8)	27 (13.0)
Most frequent AEs (>10% all grade in either arm), n (%)		
Diarrhea	34 (16.7)	40 (19.3)
Neutropenia	40 (19.6)	32 (15.5)
Anemia	27 (13.2)	31 (15.0)
Upper respiratory tract infection	44 (21.6)	29 (14.0)
Arthralgia	19 (9.3)	29 (14.0)
Hypertension	32 (15.7)	27 (13.0)
Muscle spasms	6 (2.9)	23 (11.1)
Contusion	21 (10.3)	18 (8.7)
Urinary tract infection	22 (10.8)	17 (8.2)
Cough	26 (12.7)	13 (6.3)

AE, adverse event.

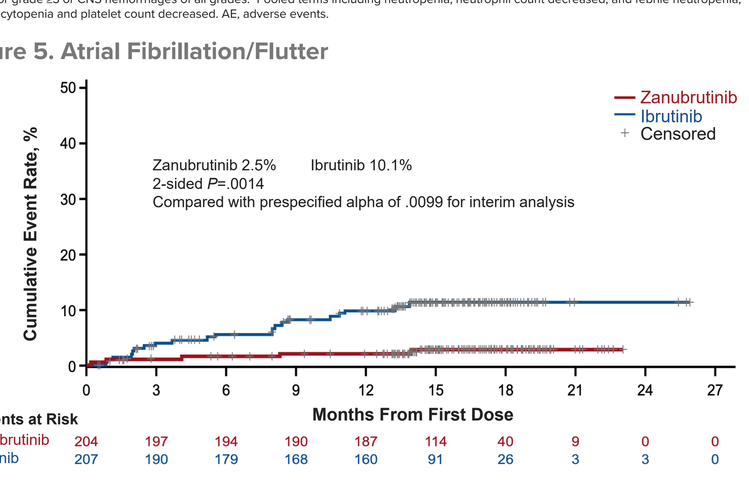
- Of the additional AEs of special interest, cardiac disorders of any grade, and of grade 3 or higher, were more frequently reported in the ibrutinib arm versus the zanubrutinib arm (**Table 4**)
- Atrial fibrillation and flutter, a key secondary endpoint, was experienced by 10.1% of patients in the ibrutinib arm compared with 2.5% in the zanubrutinib arm for any grade (2 sided *P*=.0014)
- The rate of atrial fibrillation and flutter were consistently higher in the ibrutinib arm over time (**Figure 5**)
- Rate of neutropenia (including neutropenia, neutrophil count decreased, and febrile neutropenia) was numerically higher with zanubrutinib at 28.4% versus 21.7% with ibrutinib
- Grade ≥3 infections were numerically lower with zanubrutinib at 12.7% versus 17.9% with ibrutinib

Table 4. Additional AEs of Special Interest

	Zanubrutinib (n=204)		Ibrutinib (n=207)	
Safety Analysis Population	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Cardiac disorders[a], n (%)	28 (13.7)	5 (2.5)	52 (25.1)	14 (6.8)
Atrial fibrillation and flutter (key 2° endpoint), n (%)	**5 (2.5)**	**2 (1.0)**	**21 (10.1)**	**4 (1.9)**
Hemorrhage, n (%)	73 (35.8)	6 (2.9)	75 (36.2)	6 (2.9)
Major hemorrhage[b], n (%)	6 (2.9)	6 (2.9)	8 (3.9)	6 (2.9)
Hypertension, n (%)	34 (16.7)	22 (10.8)	34 (16.4)	22 (10.6)
Infections, n (%)	122 (59.8)	26 (12.7)	131 (63.3)	37 (17.9)
Neutropenia[c], n (%)	58 (28.4)	38 (18.6)	45 (21.7)	31 (15.0)
Thrombocytopenia[c], n (%)	19 (9.3)	7 (3.4)	26 (12.6)	7 (3.4)
Secondary primary malignancies, n (%)	17 (8.3)	10 (4.9)	13 (6.3)	4 (1.9)
Skin cancers, n (%)	7 (3.4)	3 (1.5)	10 (4.8)	2 (1.0)

[a]Cardiac disorders leading to treatment discontinuation: zanubrutinib 0 patients and ibrutinib 7 (3.4%) patients. [b]Includes hemorrhages that were serious or grade ≥3 or CNS hemorrhages of all grades. [c]Pooled terms including neutropenia, neutrophil count decreased, and febrile neutropenia; thrombocytopenia and platelet count decreased. AE, adverse events.

Figure 5. Atrial Fibrillation/Flutter



CONCLUSIONS

- In this interim analysis of a randomized, phase 3 ALPINE study in patients with relapsed/refractory CLL/SLL, zanubrutinib, compared with ibrutinib, was shown to have:
  - A superior response rate (ORR of 78.3% for zanubrutinib versus 62.5% for ibrutinib, 2-sided *P*=.0006)
  - An improved PFS (94.9% for zanubrutinib versus 84% for ibrutinib, 2-sided *P*=.0007)
  - A lower rate of atrial fibrillation/flutter (2.5% for zanubrutinib versus 10.1% for ibrutinib, 2-sided *P*=.0014)
- These data support that more selective BTK inhibition, with more complete and sustained BTK occupancy, results in improved efficacy and safety outcomes

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