LXIV Congreso Nacional SEHH
XXXVIII Congreso Nacional SETH
38th World Congress of the International Society of Hematology (ISH)
BARCELONA
6 - 8 | OCT | 2022
PALACIO DE CONGRESOS DE BARCELONA

First Interim Analysis of ALPINE Study: Results of a Phase 3 Randomized Study of Zanubrutinib vs Ibrutinib in Patients with Relapsed/Refractory CLL/SLL

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Disclosures for Luis Felipe Casado

- Consultancy: Janssen, Roche, Novartis, BMS, Amgen, Takeda, Pfizer, Incyte, Abbvie, GSK, Sanofi, BeiGene

- Research funding: Janssen, Roche, Novartis, BMS, Amgen, Takeda, Pfizer, Incyte, Abbvie, GSK, Sanofi, BeiGene, Loxo

Background

- Treatment of CLL/SLL has been transformed with the advent of effective inhibitors of B-cell receptor signaling[1,2], such as the BTK inhibitor ibrutinib[3,4]
- 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[5]
- We hypothesized that zanubrutinib may minimize toxicities related to ibrutinib off-target inhibition[6], and zanubrutinib[5] may improve efficacy outcomes

BTK, Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; EGFR, epidermal growth factor receptor.

1. Aalipour A, et al. *Br J Haematol.* 2013;163:436-443; 2. Ten Hacken E, et al. *Clin Cancer Res.* 2014;20:548-556; 3. Imbruvica® (ibrutinib) [package insert]. Janssen Biotech, Inc; 2019; 4. Imbruvica® (ibrutinib) [SPC]. Janssen-Cilag International NV; 2018; 5. Tam CS, et al. *Blood.* 2019;134:851-859; 6. Coutre SE, et al. *Blood Adv.* 2019;3:1799-1807.

ALPINE: Phase 3, Randomized Study of Zanubrutinib vs Ibrutinib in Patients with R/R CLL/SLL

R/R CLL/SLL with ≥ 1 prior treatment
(Planned N = 600, Actual N = 652)

Key Inclusion Criteria

- R/R to ≥ 1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI

Key Exclusion Criteria

- Current or past Richter's transformation
- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists

R
1:1

Arm A
Zanubrutinib 160 mg BID

Arm B
Ibrutinib 420 mg QD

Stratification Factors

- Age
- Geographic region
- Refractory status
- del(17p)/*TP53* mutation status

BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CT, computed tomography; del(17p), chromosome 17p deletion; MRI, magnetic resonance imaging; QD, once daily; R, randomized; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; *TP53*, gene encoding tumor protein p53.

Baseline Patient and Disease Characteristics

Characteristic	Zanubrutinib (n = 207)	Ibrutinib (n = 208)
Age, median (range)	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 PS ≥ 1, n (%)	128 (61.8)	132 (63.5)
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*	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)

- 30 patients have been enrolled from 10 sites across Spain
- Treatment arms were well balanced for demographic and disease characteristics
- 19.8% in the zanubrutinib arm compared with 18.3% in the ibrutinib arm had del(17p) and/or *TP53* mutated

[a]2 patients with missing values.
del(17p), chromosome 17p deletion; del(11q), chromosome 11q deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; *TP53*, gene encoding tumor protein p53.

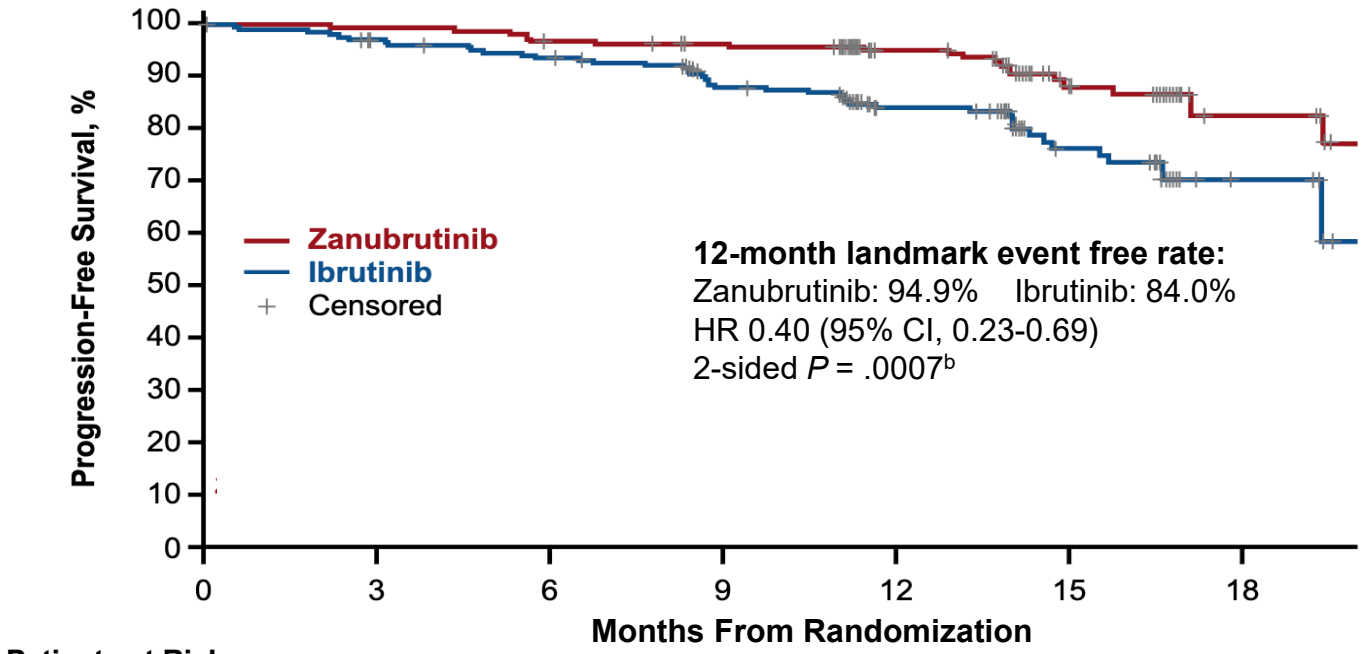
ORR by Investigator Assessment

	Zanubrutinib (n = 207), n (%)	Ibrutinib (n = 208), n (%)
Primary endpoint: ORR (PR + CR)	162 (**78.3**) 95% CI: 72.0, 83.7	130 (**62.5**) 95% CI: 55.5, 69.1
	Superiority 2-sided *P* = .0006 compared with pre-specified alpha of 0.0099	
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), n (%)	**del(17p) (n = 26), n (%)**
ORR (PR + CR)	20 (83.3)	14 (53.8)

- After a median follow-up of 15 months, ORR was significantly higher with zanubrutinib (78.3%) vs ibrutinib (62.5%)
- In the subset of patients with del(17p), ORR was even higher for zanubrutinib (83.3%) vs ibrutinib (53.8%)

CI, confidence interval; CR, complete response; CRi, complete response with incomplete bone marrow recovery; del(17p), chromosome 17p deletion; 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 Investigator Assessment[a]



Patients at Risk							
Zanubrutinib	207	200	194	190	152	70	19
Ibrutinib	208	196	188	170	125	57	8

- 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

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

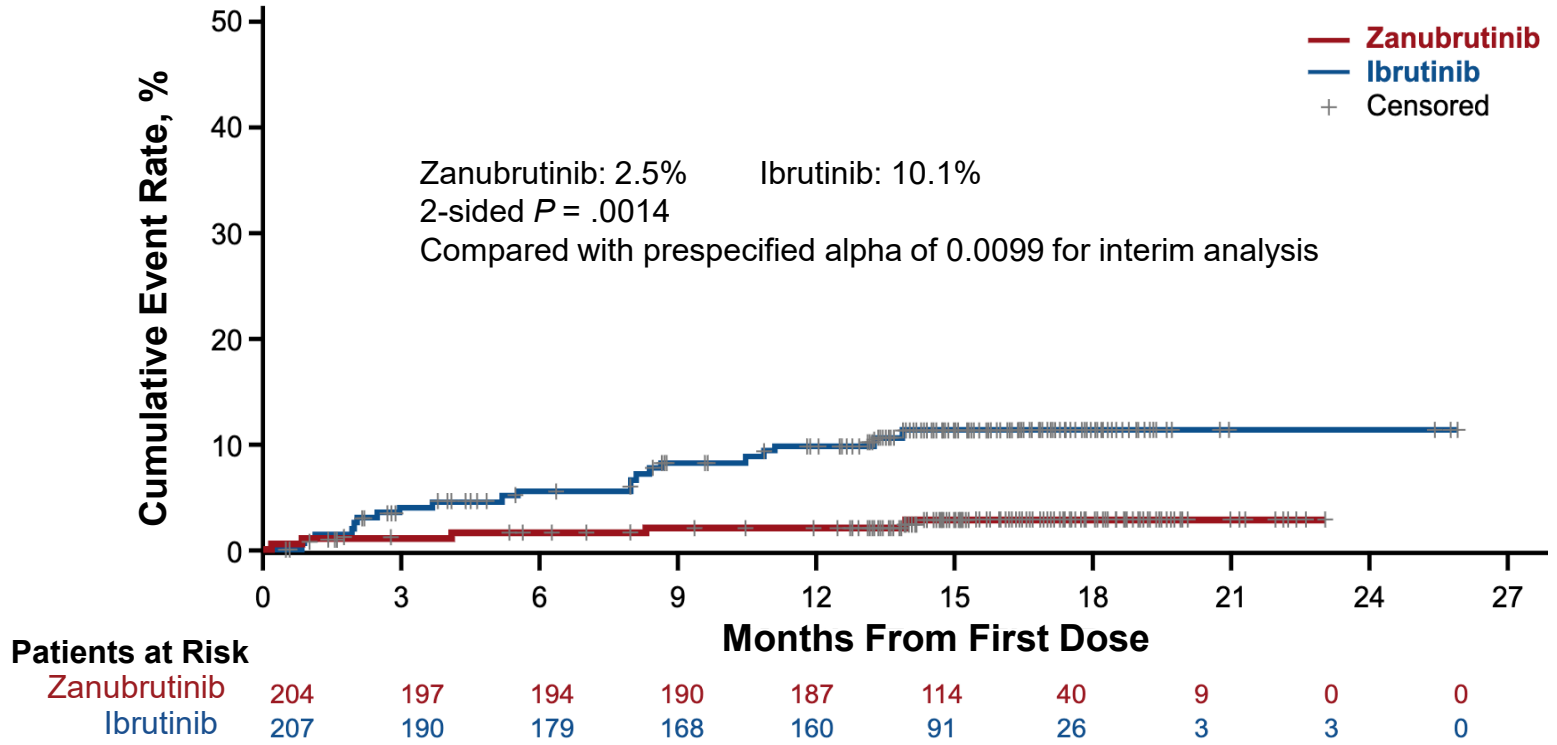
Safety Summary

Safety Analysis Population, 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 patients experienced an AE, regardless of treatment arm
- Serious or fatal AEs were numerically higher in the ibrutinib vs the zanubrutinib arm, and the rate of AEs leading to treatment discontinuation was lower with zanubrutinib

AE, adverse event.

Atrial Fibrillation/Flutter



- Atrial fibrillation and flutter were more frequently reported with ibrutinib (10.1%) vs zanubrutinib (2.5%); the rate was consistently higher in the ibrutinib arm over time

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
  - An improved PFS
  - A lower rate of atrial fibrillation/flutter
- These data support that more selective BTK inhibition, with more complete and sustained BTK occupancy results in improved efficacy and safety outcomes

Acknowledgments

We would like to thank the investigators, site support staff, and especially the patients and their caregivers for participating in this study. Participating countries: Australia, China, New Zealand, Belgium, Czech Republic, France, Germany, Italy, Poland, Spain, Sweden, The Netherlands, Turkey, United Kingdom and United States.

This study was sponsored by BeiGene.

Editorial support was provided by Medical Expressions and funded by BeiGene.

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