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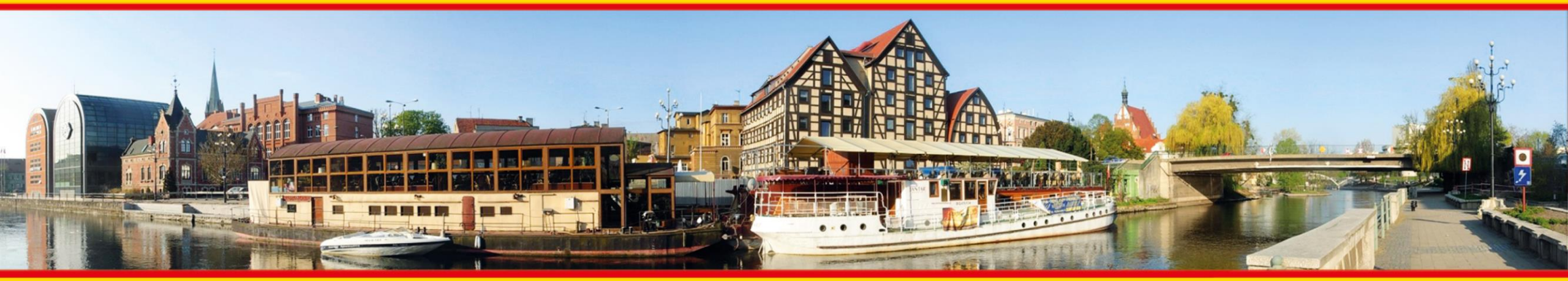

First Interim Analysis of ALPINE Study: Results of a Phase 3 Randomized Study of Zanubrutinib vs Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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Disclosures for Wojciech Jurczak

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Background

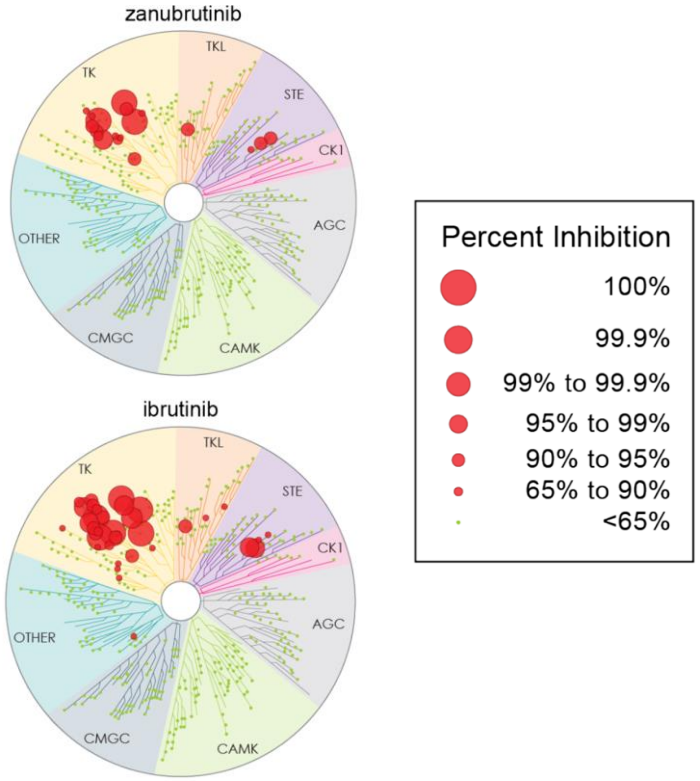
- Treatment of CLL/SLL has been transformed with the advent of effective inhibitors of B-cell receptor signaling[1,2], such as the BTK inhibitor ibrutinib[3,4]
- Zanubrutinib is an irreversible, potent, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition 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.

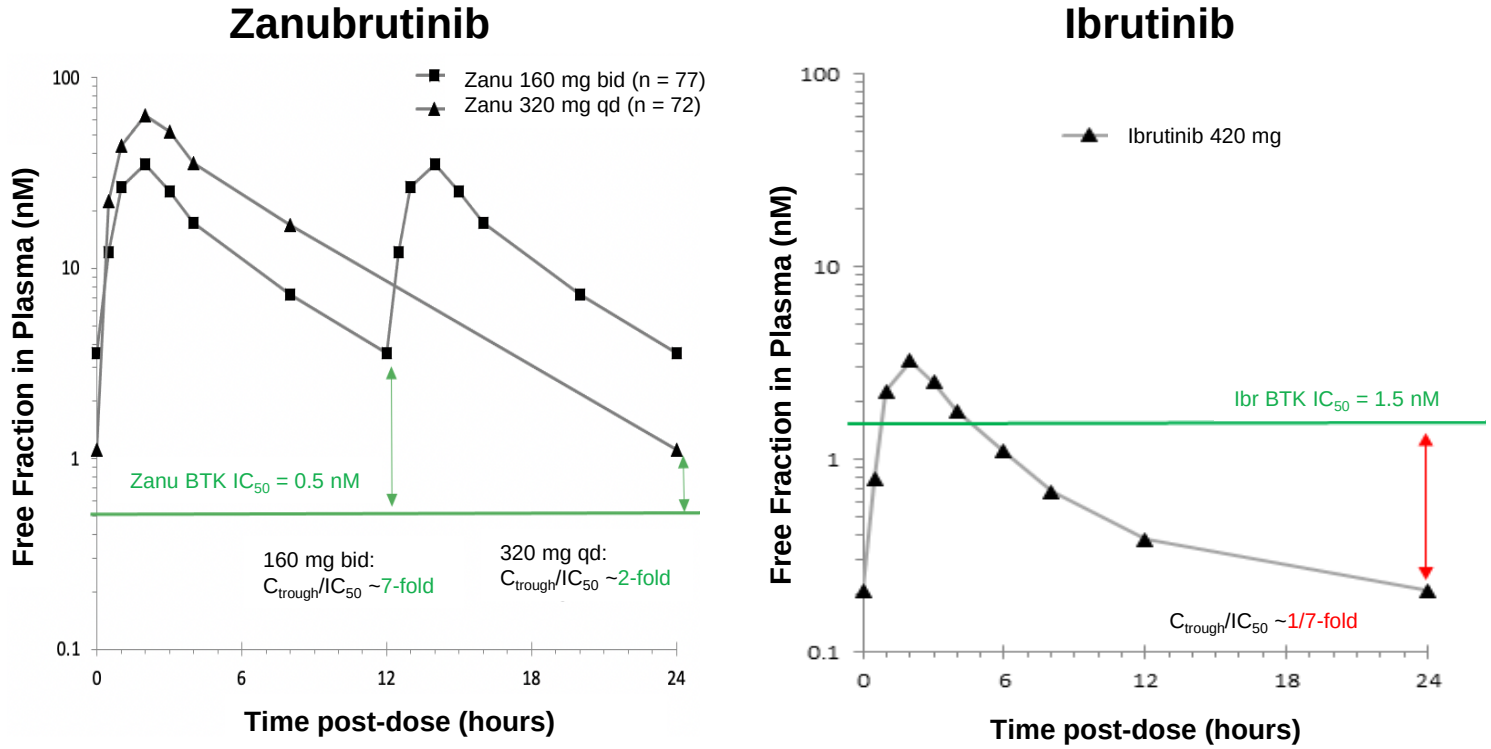
1. Aalipour A, et al. *Br J Haematol.* 2013;163(4):436-443; 2. ten Hacken E, et al. *Clin Cancer Res.* 2014;20(3):548-556; 3. Imbruvica® (ibrutinib) [package insert]. Janssen Biotech, Inc; 2019; 4. Imbruvica® (ibrutinib) [SPC]. Janssen-Cilag International NV; 2018; 5. Tam C, et al. *Blood.* 2019;134(11):851-859; 6. Coutre S, et al. *Blood Adv.* 2019;3(12):1799-1807.

Pharmacokinetics and Selectivity of Zanubrutinib and Ibrutinib

Whole Kinase Panel Selectivity Profiles



Free Drug Concentration Time Profiles Relative to IC_{50}



Note: These data are from separate analyses. Limitations of cross-trial comparisons apply.

- Zanubrutinib has shown less off-target kinase inhibition, more potent BTK inhibition, and a longer time profile of free drug concentration, compared with ibrutinib

bid, twice daily; BTK, Bruton tyrosine kinase; C_{trough}, trough concentration; IC_{50}, 50% inhibitory concentration; qd, once daily

Adapted from: 1. Kaptein A, et al. *Blood.* 2018;132:1871; 2. Ou YC, et al. *Leuk Lymphoma.* 2021;62(11):2612-2624; 3. Marostica E, et al. *Cancer Chemother Pharmacol*. 2015;75(1):111-121.

ALPINE: Phase 3, Randomized Study of Zanubrutinib vs Ibrutinib in Patients with Relapsed/Refractory CLL or 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/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CT, computed tomography; del(17p), chromosome 17p deletion; MRI, magnetic resonance imaging; qd, once daily; R, randomized; R/R, relapsed/refractory; *TP53*, gene encoding tumor protein p53.

Baseline Patient and Disease Characteristics

Characteristic	Zanubrutinib (n = 207)	Ibrutinib (n = 208)
Age, median (range), years	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, 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)

- Treatment arms were well balanced for demographic and disease characteristics
- 11.6% in the zanubrutinib arm compared with 12.5% in the ibrutinib arm had del(17p)

[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

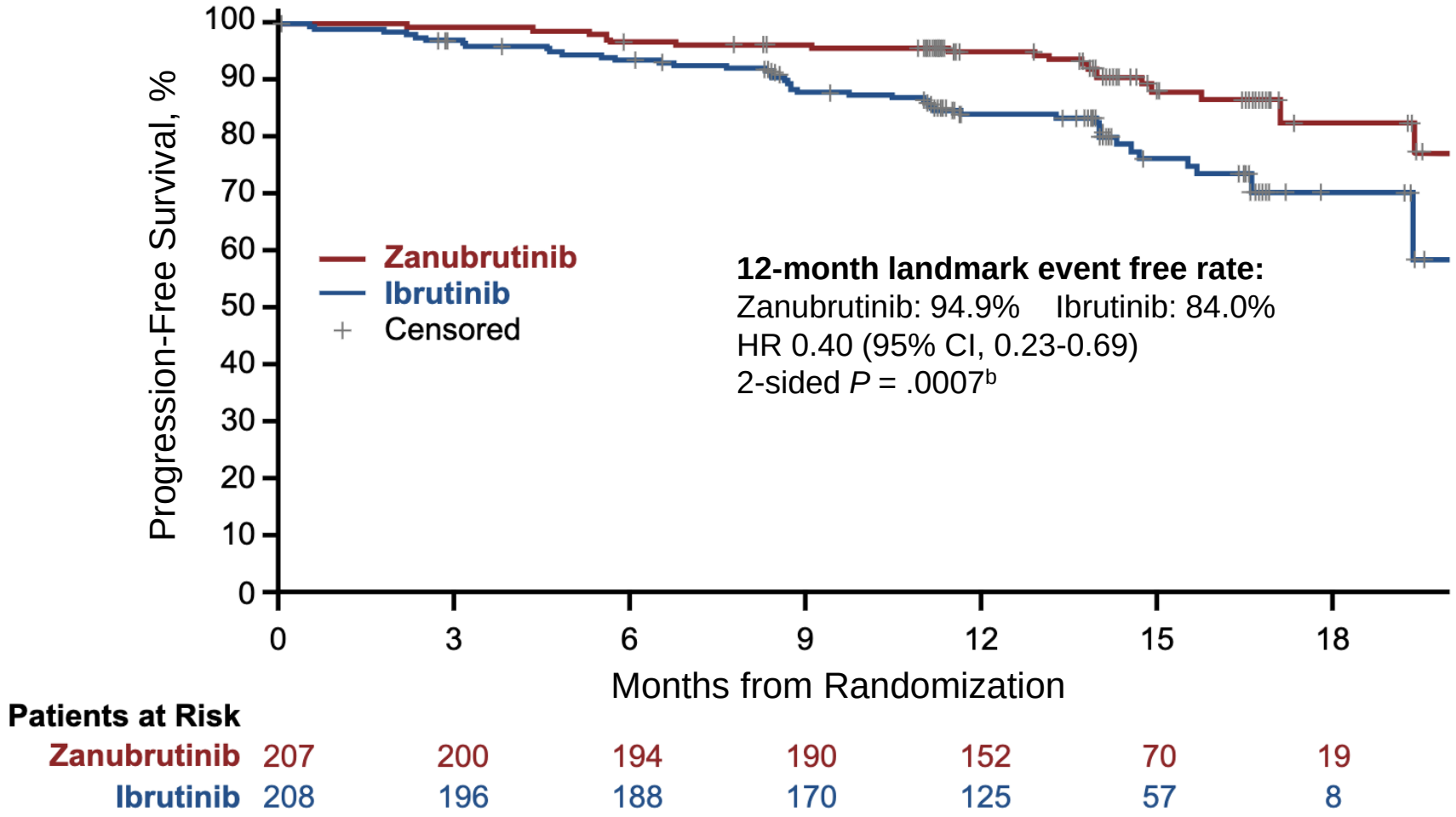
	Zanubrutinib (n = 207), n (%)	Ibrutinib (n = 208), n (%)
Primary endpoint: ORR (PR + CR)	162 (**78.3**) 95% CI: 72.0, 83.7	130 (**62.5**) 95% CI: 55.5, 69.1
	Superiority 2-sided *P* = .0006 compared with pre-specified alpha of .0099	
CR/CRi	4 (1.9)	3 (1.4)
nPR	1 (0.5)	0
PR	157 (75.8)	127 (61.1)
ORR (PR-L + 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]



- 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.

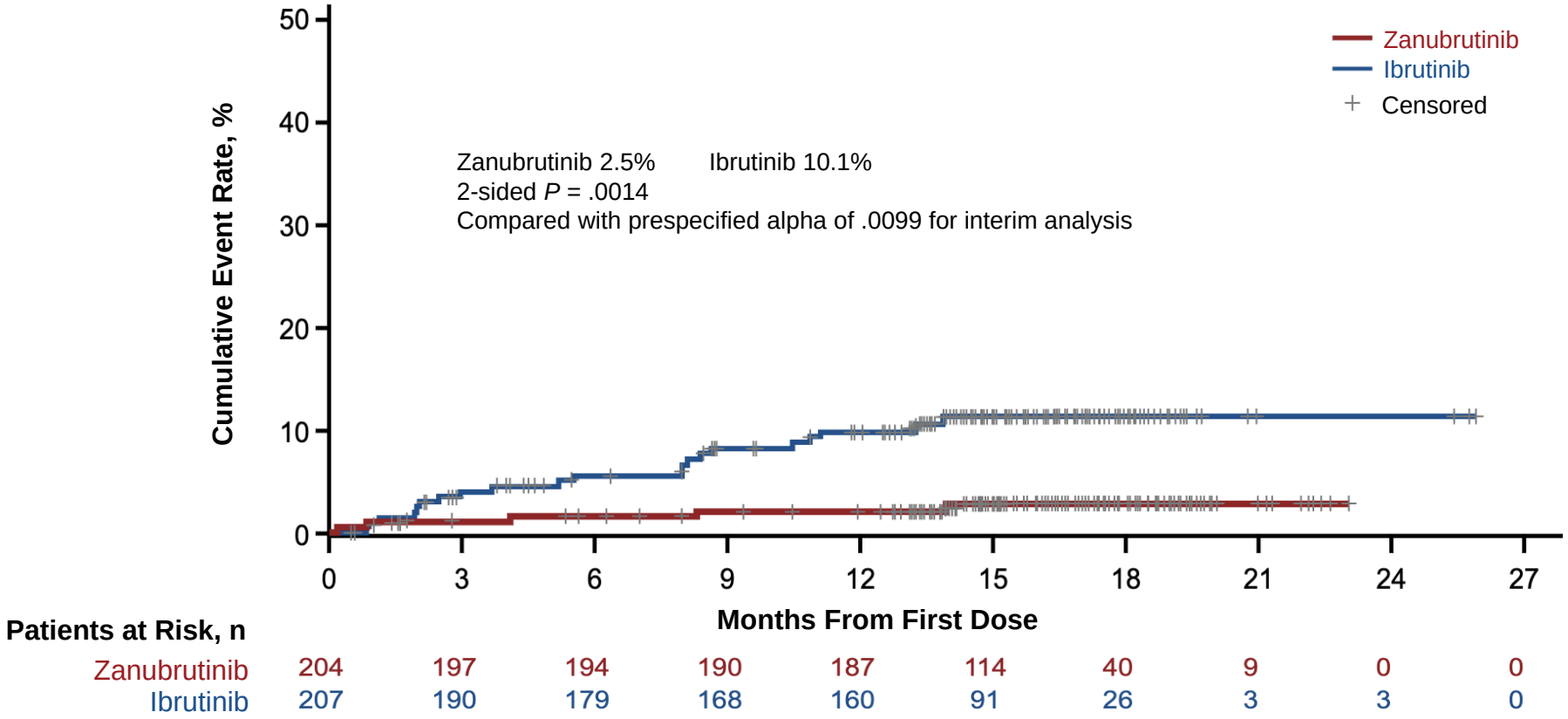
Safety Summary

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
- 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

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