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

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Background

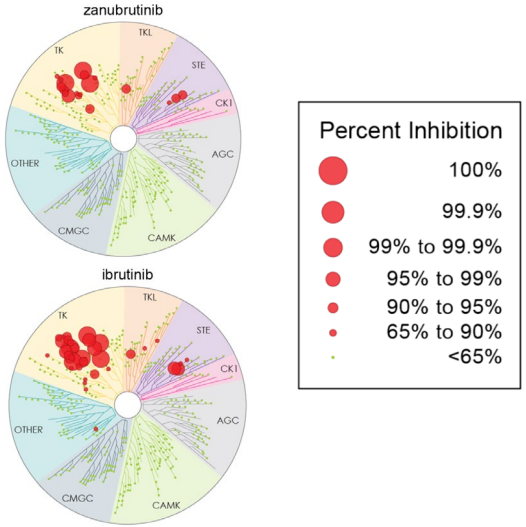
- Treatment of CLL/SLL has been transformed with the advent of effective inhibitors of B-cell receptor signaling[1,2], such as the BTK inhibitor ibrutinib[3,4]
- Zanubrutinib is an irreversible, potent, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition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

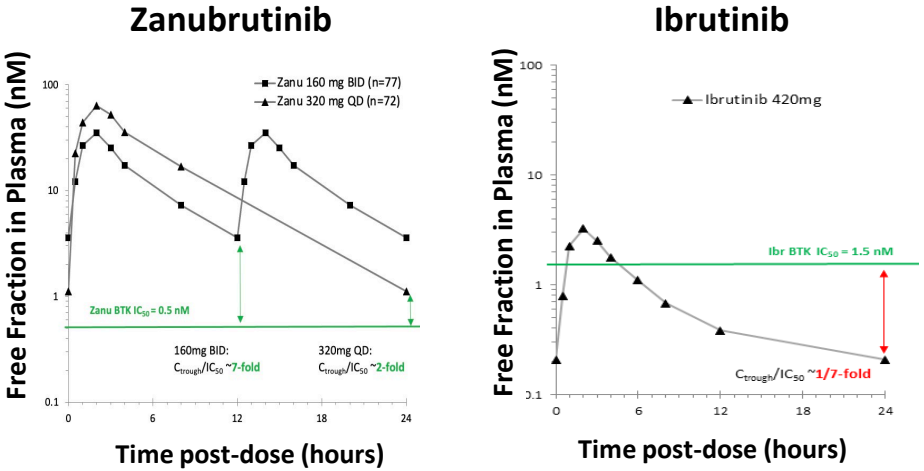
1. Aalipour A, et al. *Br J Haematol* 2013;163:436-443; 2. Ten Hacken E, et al. *Clin Cancer Res* 2014;20:548-556; 3. Imbruvica® (ibrutinib) [package insert]. Janssen Biotech, Inc; 2019; 4. Imbruvica® (ibrutinib) [SPC]. Janssen-Cilag International NV; 2018; 5. Tam CS, et al. *Blood* 2019;134:851-859;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

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;62:2612-2624; 3. Marostica E, et al. *Cancer Chemother Pharmacol*. 2015;75:111-121.

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

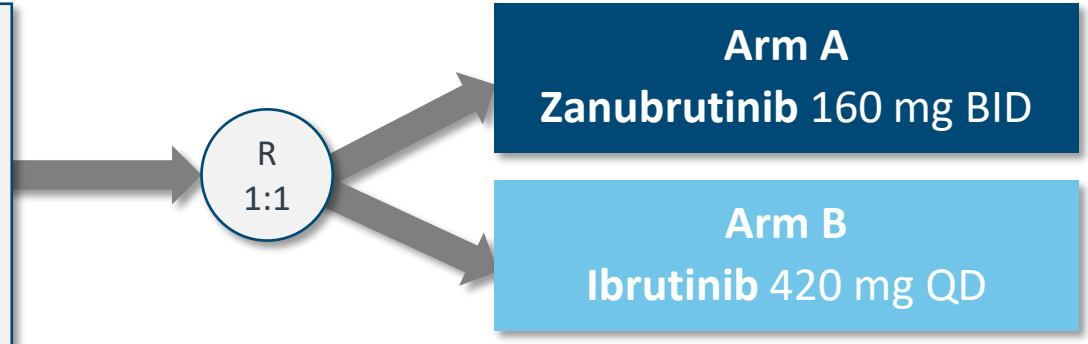
R/R CLL/SLL with ≥ 1 prior treatment
(planned N = 600, actual N = 652)

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



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.

Endpoints and Analysis

Primary endpoint

- ORR (PR + CR) noninferiority and superiority as assessed by investigator

Secondary endpoints:

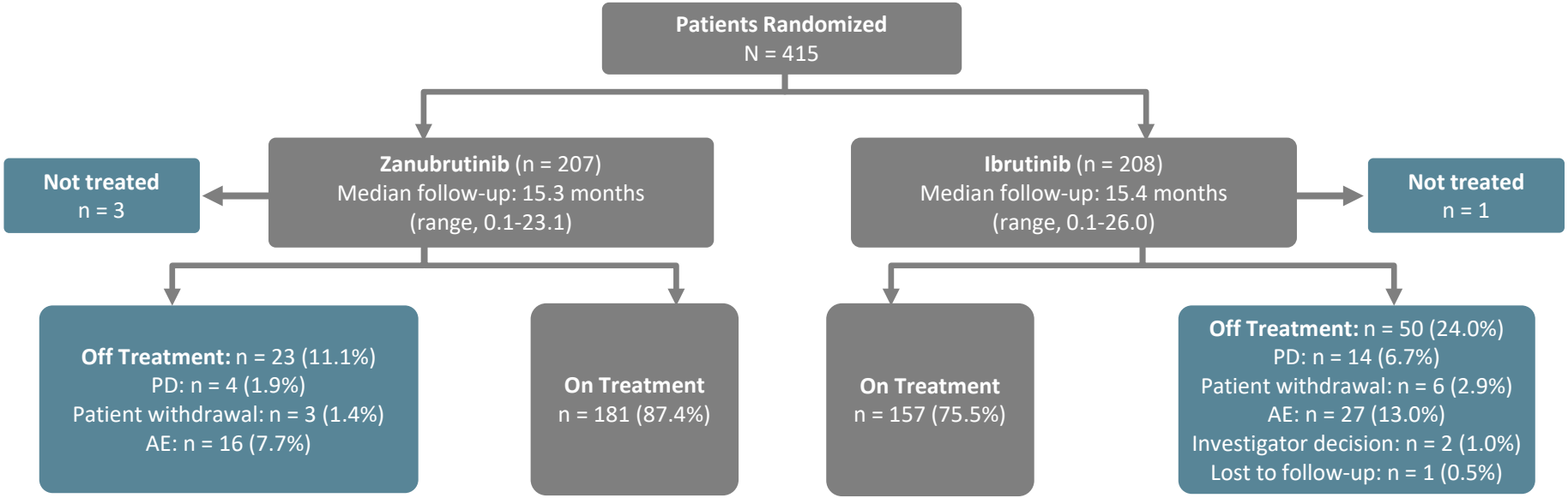
- Atrial fibrillation (any grade)
- DOR, PFS, OS
- Time to treatment failure
- PR-L or higher
- Patient-reported outcomes
- Safety

Preplanned interim analysis

- Data cutoff approximately 12 months after the randomization of 415 patients
- Data presented here are for the first 415 patients, and efficacy results are per investigator assessment

CR, complete response; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PR-L, partial response with lymphocytosis.

Patient Disposition



- Between November 5, 2018, and December 20, 2019, 415 patients were randomized
- 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 remained on treatment

AE, adverse event; PD, progressive disease.

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)

- 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 Superiority 2-sided *P* = .0006 compared with pre-specified alpha of 0.0099	130 (**62.5**) 95% CI: 55.5, 69.1
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)

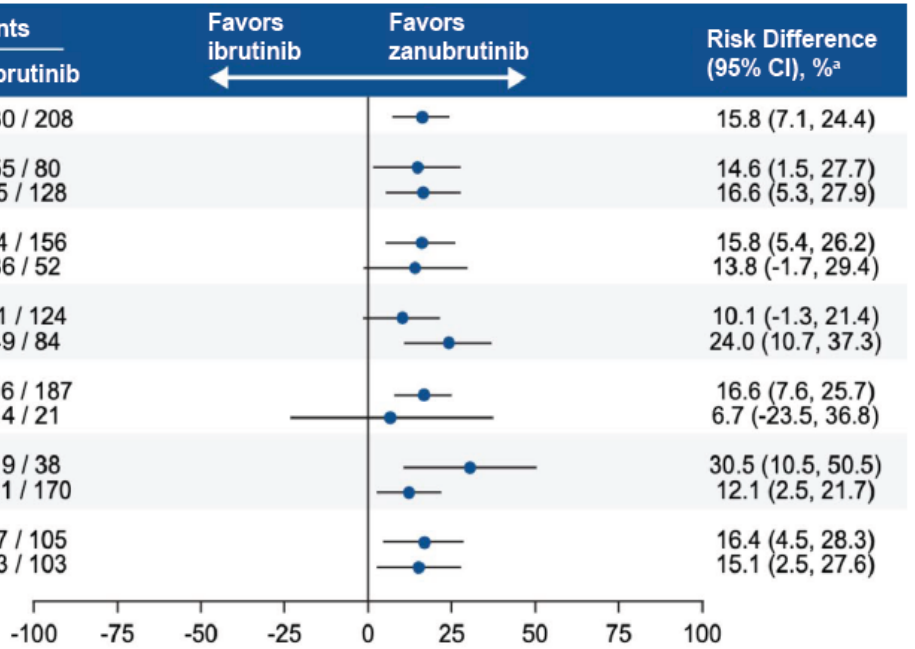
- After a median follow-up of 15 months, ORR was significantly higher with zanubrutinib (78.3%) vs ibrutinib (62.5%)
- In the subset of patients with del(17p), ORR was even higher for zanubrutinib (83.3%) vs ibrutinib (53.8%)

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.

ORR by Investigator Assessment – Key Patient Subgroups

- 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

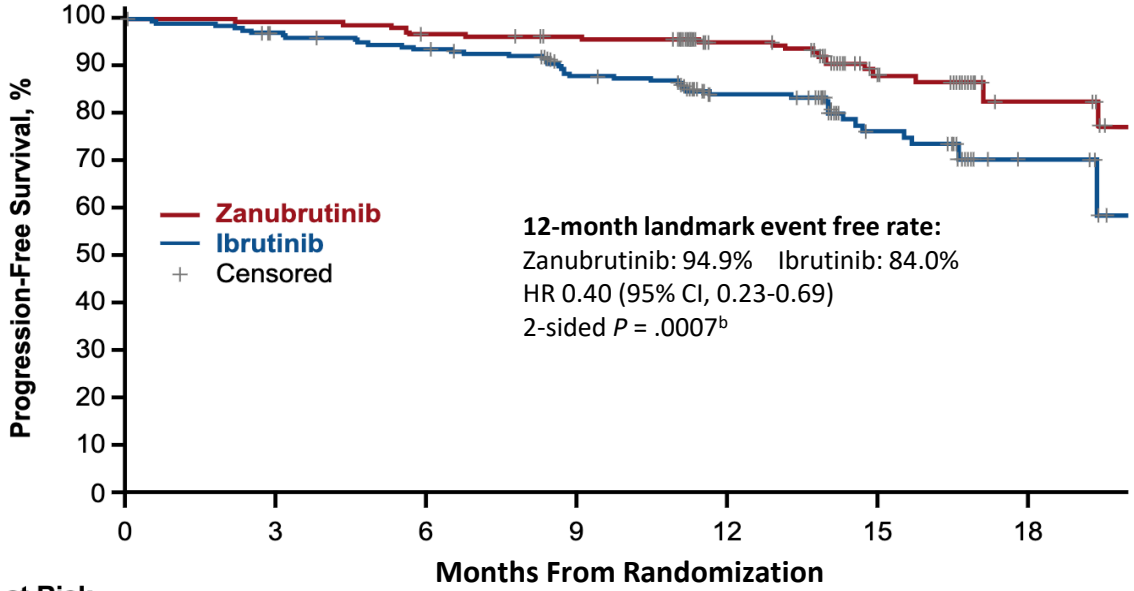
Subgroup	Response/Patients		Risk Difference (95% CI), %[a]
	Zanubrutinib	Ibrutinib	
All patients	162 / 207	130 / 208	15.8 (7.1, 24.4)
Age group			
<65 years	65 / 78	55 / 80	14.6 (1.5, 27.7)
≥65 years	97 / 129	75 / 128	16.6 (5.3, 27.9)
Sex			
Male	108 / 142	94 / 156	15.8 (5.4, 26.2)
Female	54 / 65	36 / 52	13.8 (-1.7, 29.4)
Disease stage			
Binet stage of A/B or Ann Arbor stage I/II bulky	92 / 122	81 / 124	10.1 (-1.3, 21.4)
Binet stage C or Ann Arbor stage III/IV	70 / 85	49 / 84	24.0 (10.7, 37.3)
Prior lines of therapy			
1-3	151 / 192	116 / 187	16.6 (7.6, 25.7)
>3	11 / 15	14 / 21	6.7 (-23.5, 36.8)
Baseline del(17p)/*TP53* mutation status			
Present	33 / 41	19 / 38	30.5 (10.5, 50.5)
Absent	127 / 164	111 / 170	12.1 (2.5, 21.7)
Bulky disease			
Yes	85 / 106	67 / 105	16.4 (4.5, 28.3)
No	77 / 101	63 / 103	15.1 (2.5, 27.6)



[a]Unstratified rate difference and 95% CI.

CI, confidence interval; del(17p), chromosome 17p deletion; ORR, overall response rate; *TP53*, gene encoding tumor protein p53.

PFS by Investigator Assessment[a]

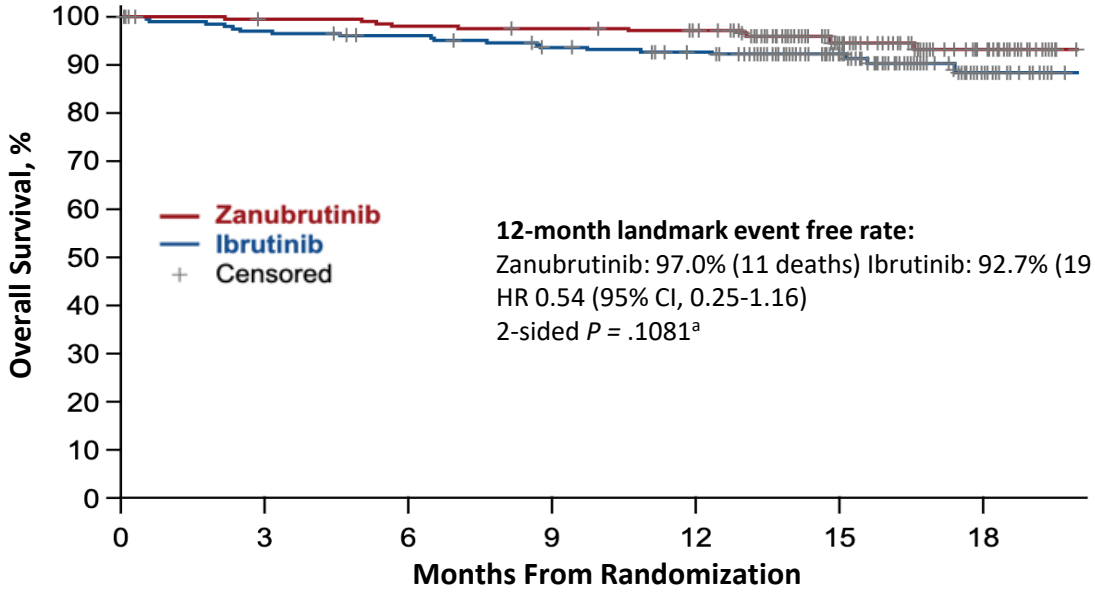


Patients at Risk

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

[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.

Overall Survival



12-month landmark event free rate:
Zanubrutinib: 97.0% (11 deaths) Ibrutinib: 92.7% (19 deaths)
HR 0.54 (95% CI, 0.25-1.16)
2-sided *P* = .1081[a]

Patients at Risk

Zanubrutinib	207	202	199	197	193	117	41
Ibrutinib	208	201	196	188	180	106	33

[a]Not a prespecified analysis.
CI, confidence interval, HR, hazard ratio.

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.

Most Frequent AEs (> 10% All Grade in Either Arm)

Safety Analysis Population, n (%)	Zanubrutinib (n = 204)	Ibrutinib (n = 207)
Patients with any AE	195 (95.6)	205 (99.0)
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.

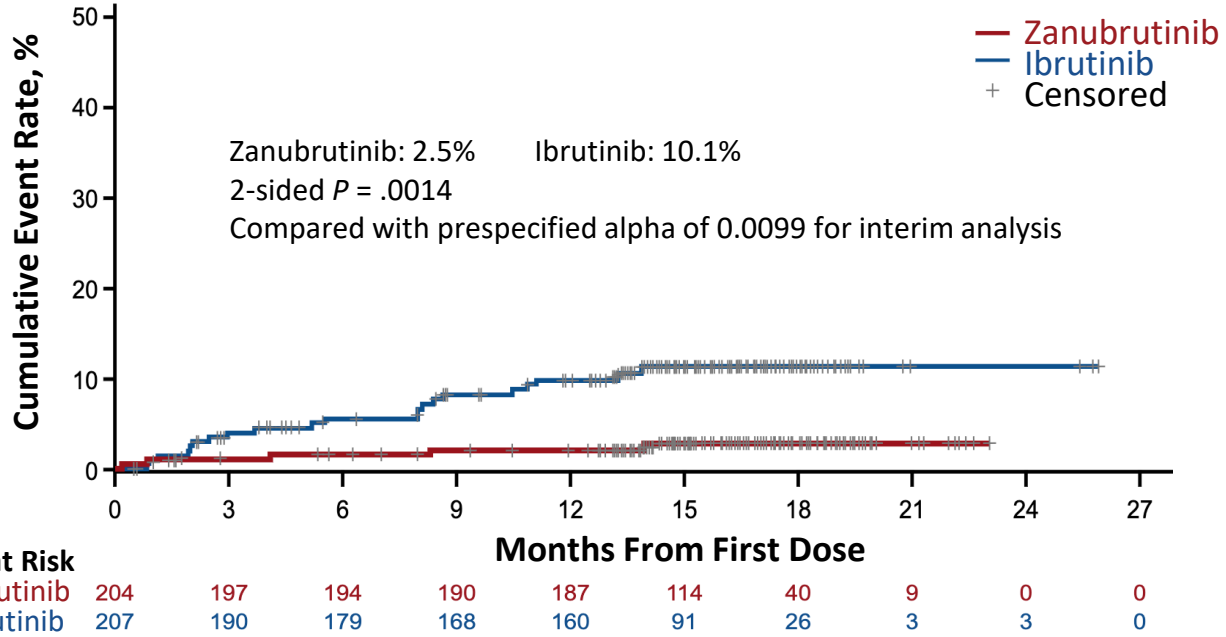
Additional AEs of Special Interest[a]

- Cardiac disorders of any grade were more frequently reported in the ibrutinib vs the zanubrutinib arm

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

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

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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