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First Interim Analysis Results of ALPINE Phase 3 Study of Zanubrutinib vs Ibrutinib in R/R Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

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COI disclosure

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Background

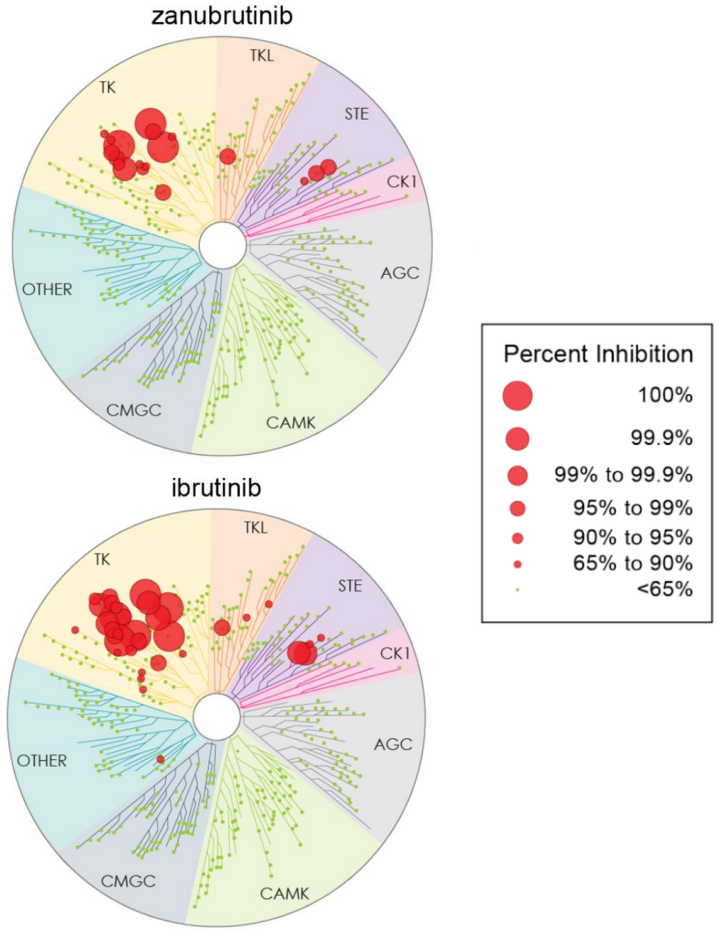
- Treatment of CLL/SLL has been transformed with the advent of effective inhibitors of B-cell receptor signaling[1,2], such as the BTK inhibitor ibrutinib[3,4]
- Zanubrutinib is an irreversible, potent, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize inhibition of TEC- and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

1. Aalipour A, Advani RH. *Br J Haematol.* 2013;163:436-443. 2. Ten Hacken E, Burger JA. *Clin Cancer Res*. 2014;20:548-556.
3. Imbruvica (ibrutinib) [package insert]. Sunnyvale, CA, USA: Pharmacyclics LLC and Horsham, PA, USA: Janssen Biotech, Inc; 2019.
4. Imbruvica (ibrutinib) [SPC]. Beerse, Belgium: Janssen-Cilag International NV; 2018. 5. Tam CS, et al. *Blood*. 2019;134:851-859. 6. Coutre S, et al. *Blood Adv*. 2019;3:1799-807.

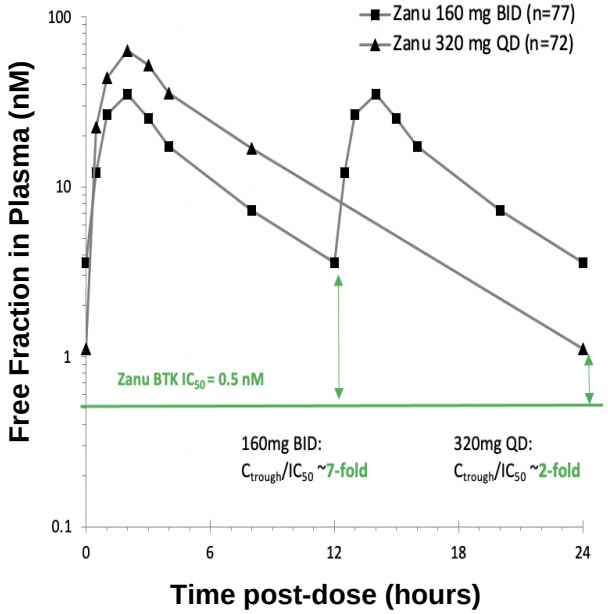
Pharmacokinetics and Selectivity of Zanubrutinib and Ibrutinib

Whole Kinase Panel Selectivity Profiles

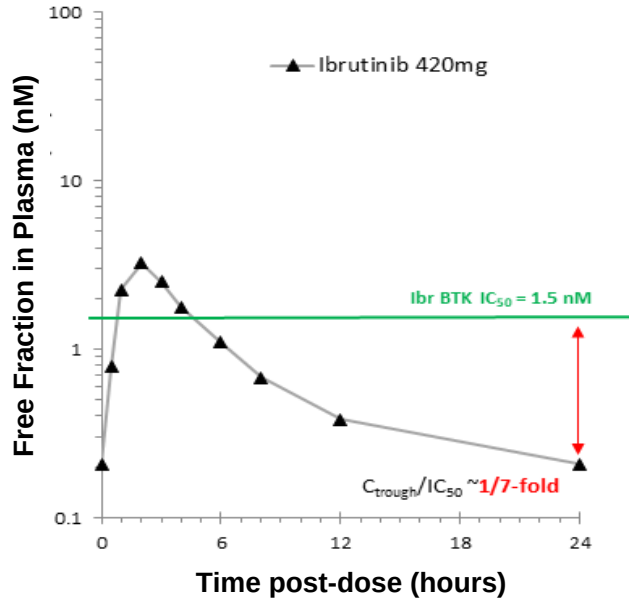


Free Drug Concentration Time Profiles Relative to IC_{50}

Zanubrutinib



Ibrutinib



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

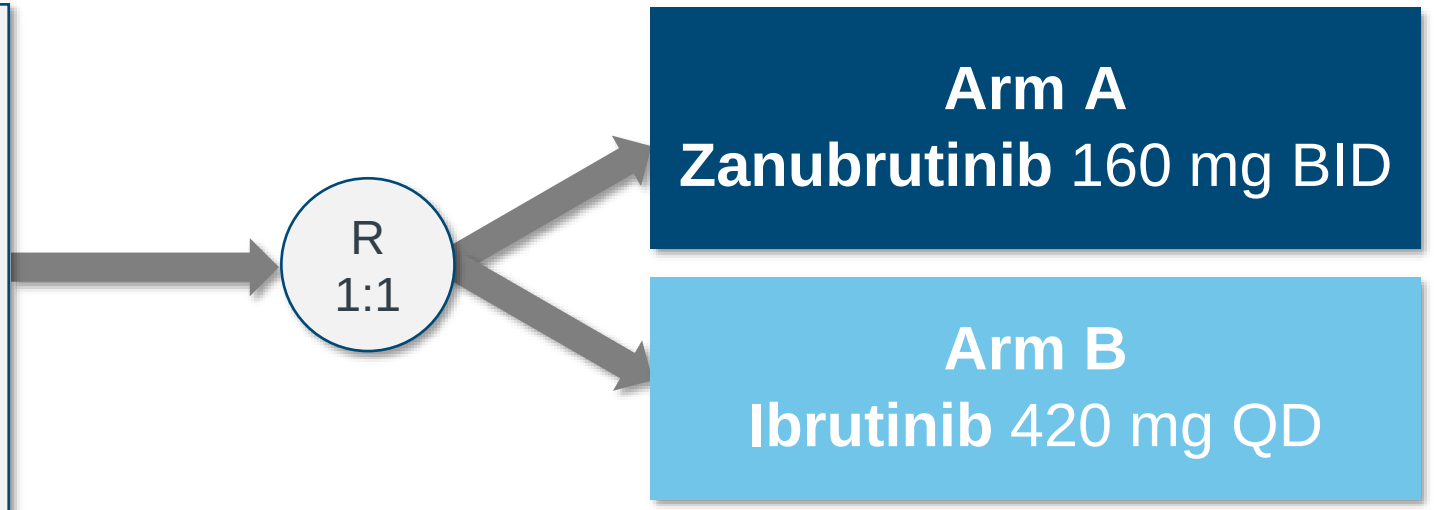
Adapted from: 1. Kaptein, et al. *Blood.* 2018;132:1871. 2. Ou, et al. *Leuk Lymphoma.* 2021;62:2612-2624. 3. Marostica, et al. *Cancer Chemother Pharmacol*. 2015;75:111-121.

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; MRI, magnetic resonance imaging; QD, once daily; R, randomized; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

Endpoints and Analysis

Primary endpoint

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

Secondary endpoints:

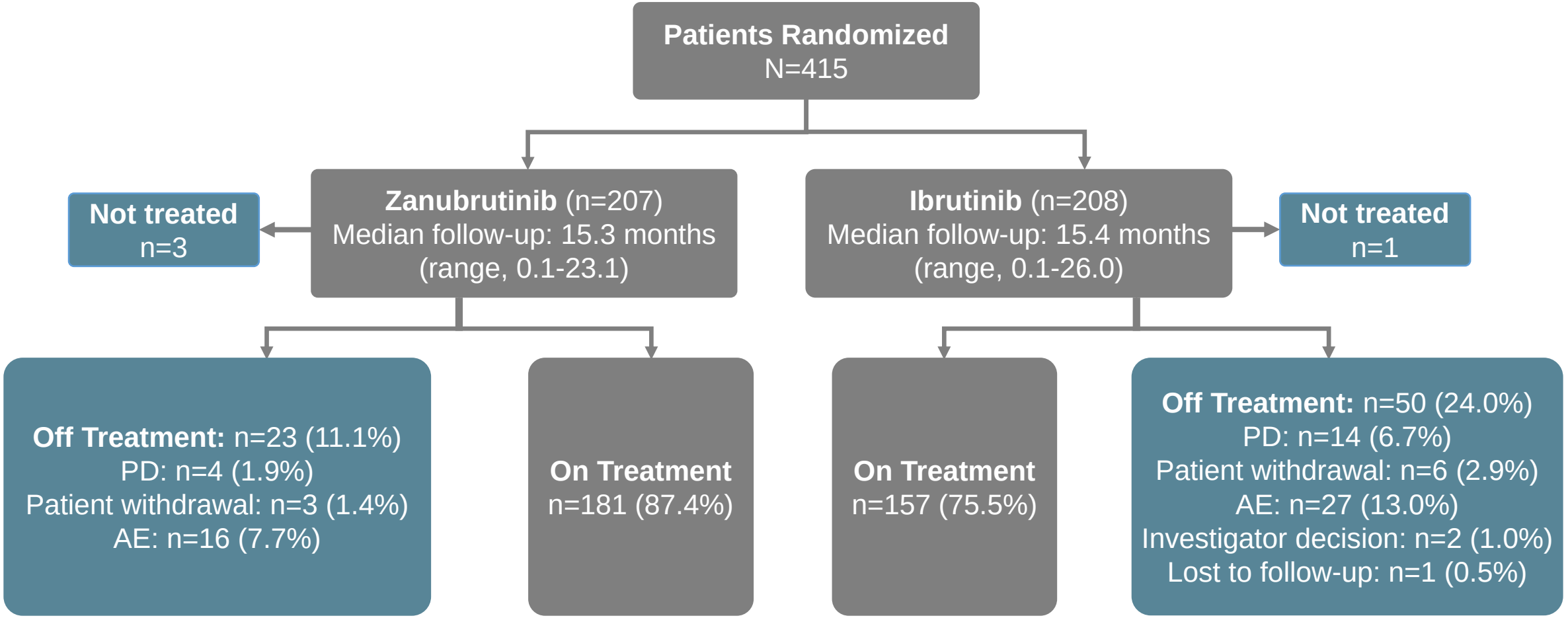
- Atrial fibrillation (any grade)
- DOR, PFS, OS
- Time to treatment failure
- PR-L or higher
- Patient-reported outcomes
- Safety

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

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

Patient Disposition



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 performance status ≥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)
del11q, n (%)	61 (29.5)	55 (26.4)
Bulky disease (≥ 5 cm), n (%)	106 (51.2)	105 (50.5)

ECOG, Eastern Cooperative Oncology Group.
[a]2 patients with missing values.

ORR by Investigator Assessment

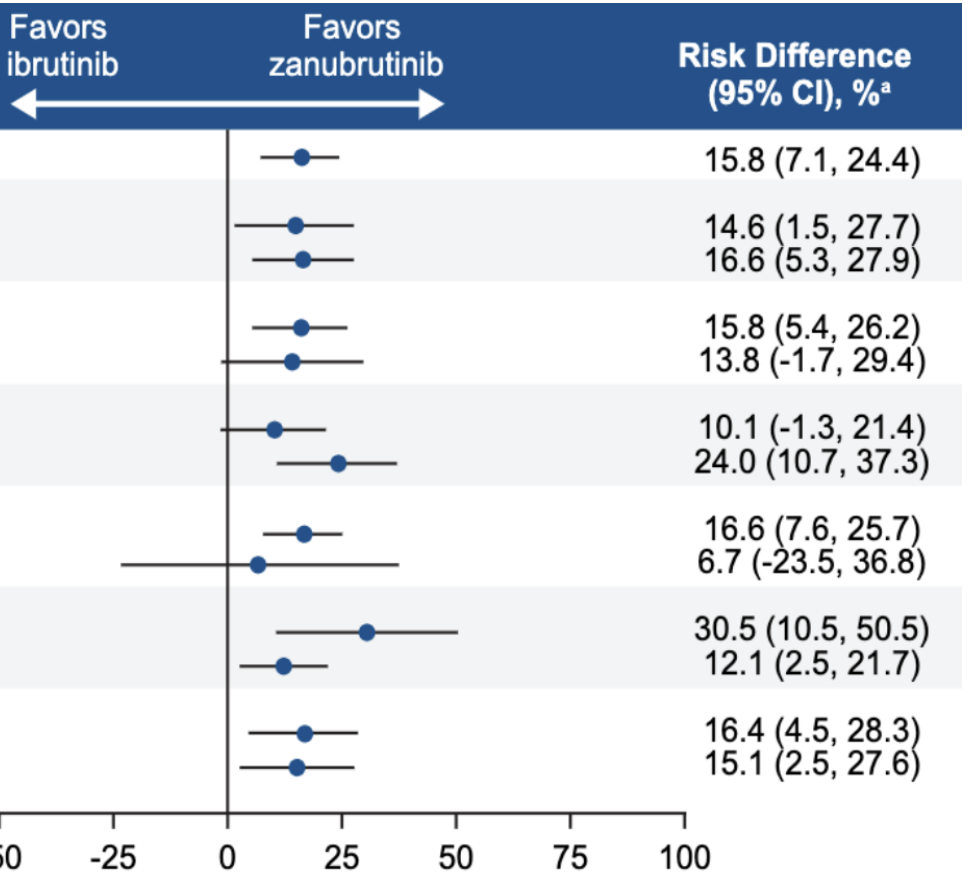
	Zanubrutinib (n=207), n (%)	Ibrutinib (n=208), n (%)
Primary endpoint: ORR (PR+CR)	162 (**78.3**) 95% CI: 72.0, 83.7	130 (**62.5**) 95% CI: 55.5, 69.1
	Superiority 2-sided *P*=0.0006 compared with pre-specified alpha of 0.0099	
CR/CRi	4 (1.9)	3 (1.4)
nPR	1 (0.5)	0
PR	157 (75.8)	127 (61.1)
ORR (PR-L+PR+CR)	*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)

CR, complete response; CRi, complete response with incomplete bone marrow recovery; D/C, discontinuation; DOR, duration of response; NE, not evaluable; nPR, nodular partial response; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

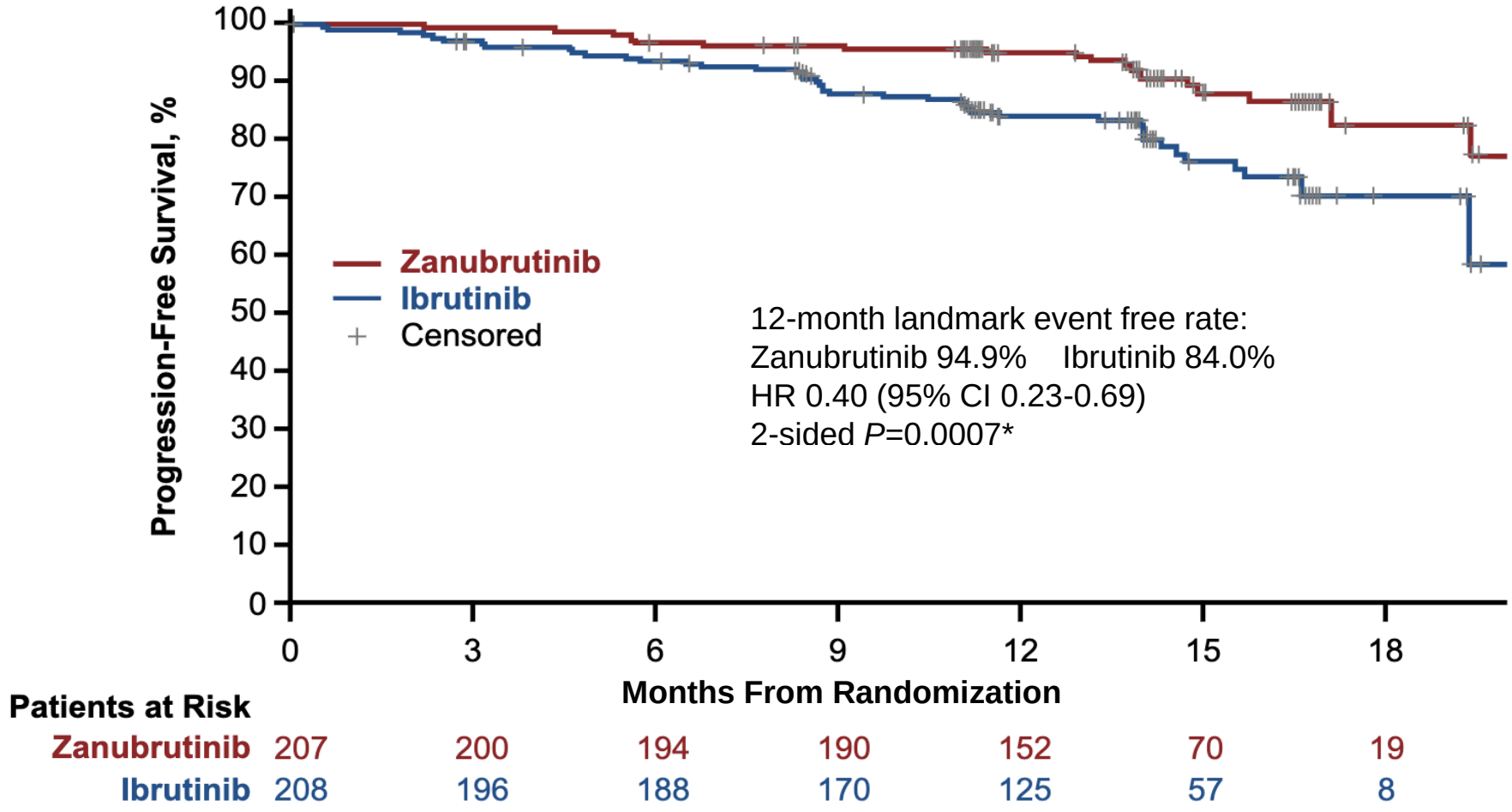
ORR by Investigator Assessment – Key Patient Subgroups

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 del17p/*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)



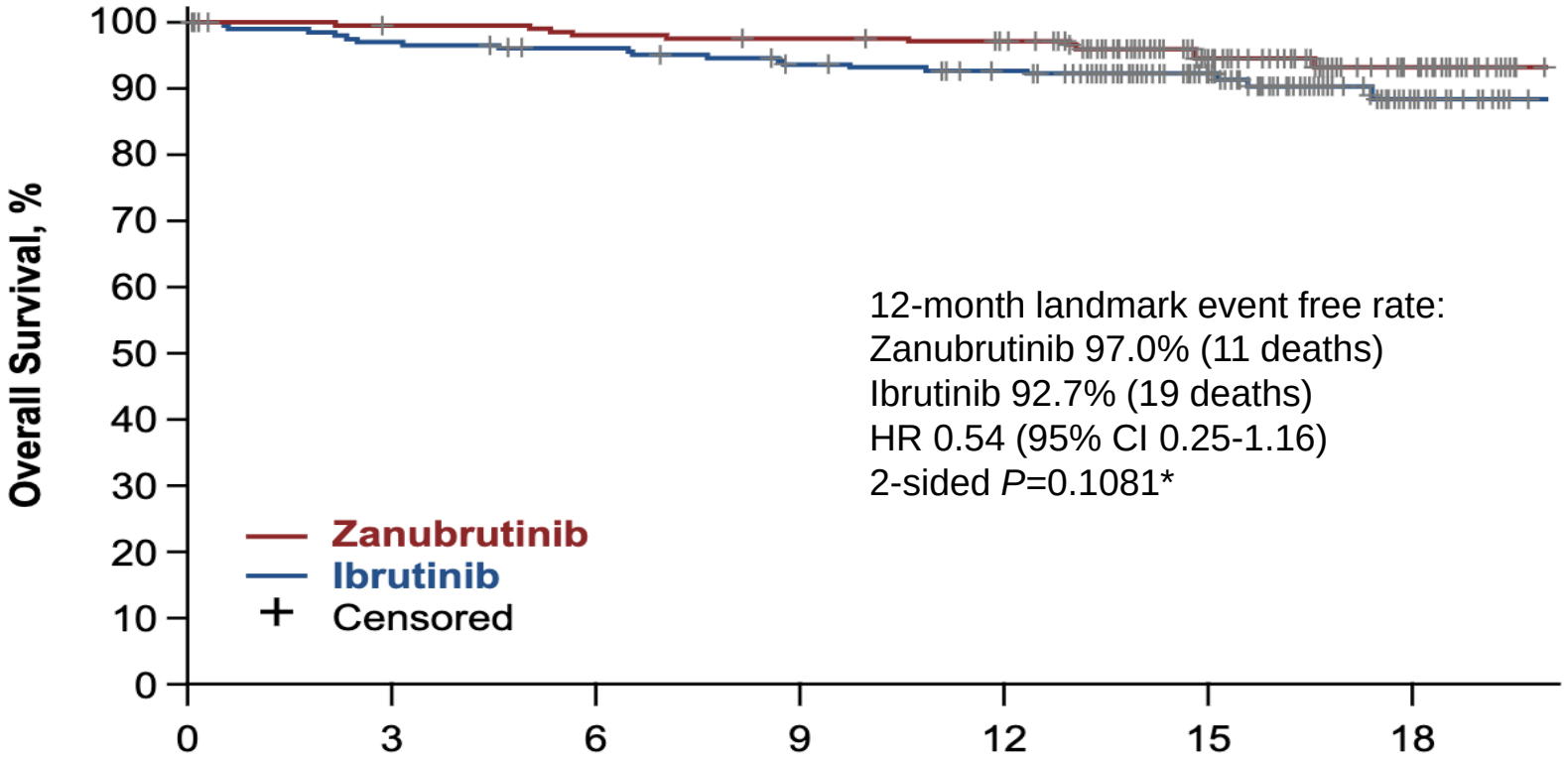
[a]Unstratified rate difference and 95% CI.

PFS by Investigator Assessment



*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.

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*=0.1081*

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

*Not a prespecified analysis

Safety Summary

Safety Analysis Population	Zanubrutinib (n=204) n (%)	Ibrutinib (n=207) n (%)
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)

AE, adverse event.

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

Safety Analysis Population	Zanubrutinib (n=204), n (%)	Ibrutinib (n=207), n (%)
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)

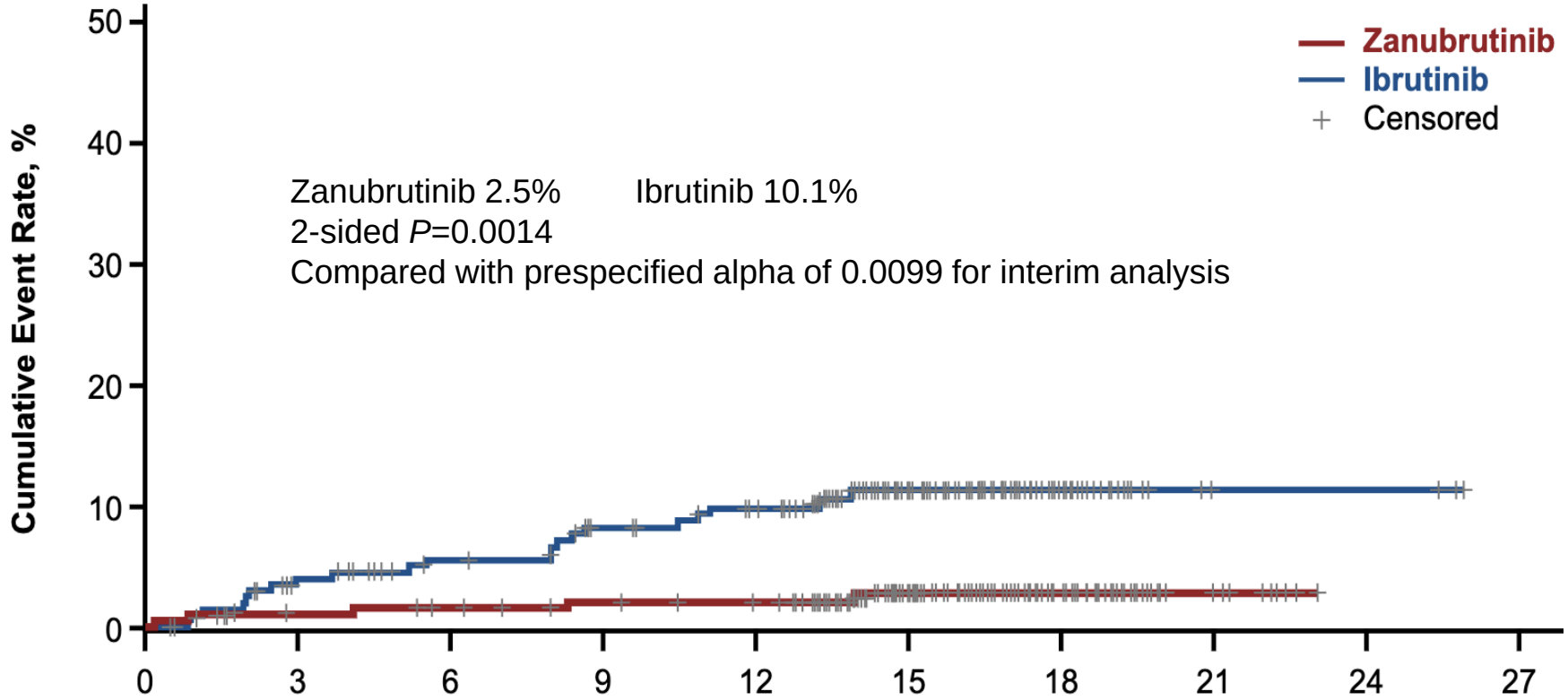
AE, adverse event.

Additional AEs of Special Interest

Safety Analysis Population	Zanubrutinib (n=204), n (%)		Ibrutinib (n=207), n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac disorders[a]	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 Major hemorrhage[b]	73 (35.8) 6 (2.9)	6 (2.9) 6 (2.9)	75 (36.2) 8 (3.9)	6 (2.9) 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[c]	58 (28.4)	38 (18.6)	45 (21.7)	31 (15.0)
Thrombocytopenia[c]	19 (9.3)	7 (3.4)	26 (12.6)	7 (3.4)
Secondary primary malignancies Skin cancers	17 (8.3) 7 (3.4)	10 (4.9) 3 (1.5)	13 (6.3) 10 (4.8)	4 (1.9) 2 (1.0)

AE, adverse events. All events are of any grade unless otherwise specified.
[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.

Atrial Fibrillation/Flutter



Patients at Risk										
Zanubrutinib	204	197	194	190	187	114	40	9	0	0
Ibrutinib	207	190	179	168	160	91	26	3	3	0

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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