Zanubrutinib Demonstrates Superior Progression-Free Survival Versus Ibrutinib For Relapsed/Refractory CLL/SLL: ALPINE Final Analysis

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Disclosures

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Bruton Tyrosine Kinase Inhibition in CLL

- B-cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation in CLL and B-cell lymphomas[1]
  - BCR signaling is dependent on Bruton's Tyrosine Kinase (BTK)
- Ibrutinib, a first-generation BTK inhibitor, transformed CLL therapy; however, it has properties that limit use[2]
  - Treatment discontinuation from toxicities has been reported in 16%-23% of patients[3-6]
  - Exposure coverage between dosing intervals falls below IC_{50} and variable BTK occupancy at trough has been observed

Ibrutinib concentration-time profile

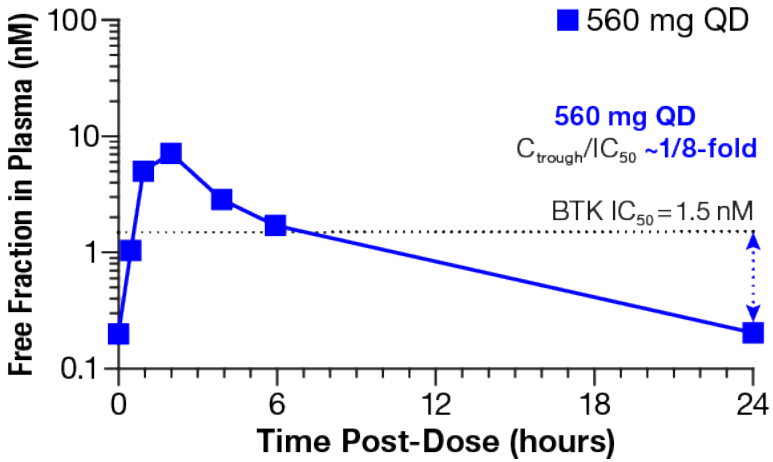


Figure adapted from Tam CS et al. *Expert Rev Clin Pharmacol*. 2021;14:11, 1329-1344

[1]Singh SP, Dammeijer F and Hendriks RW. *Molecular Cancer*. 2018; 17:57. [2]Molis S, Matures E, Tam C, Polliack A. *Hematol Oncol*. 2020; 38: 129-136. [3]Sharman JP, Black-Shinn JL, Clark J, et al. *Blood*. 2017;130(suppl 1):4060. [4]Mato AR, Nabhan C, Thompson MC, et al. *Haematologica*. 2018;103(5):874-879. [5]Munir T, Brown JR, O'Brien S, et al. *Am J Hematol*. 2019;94(12):1353-1363. [6]Ghia P, Owen C, Robak T, et al. EHA Abstract EP636 2021.

Differentiating Features of Zanubrutinib

- Zanubrutinib is a second-generation BTK inhibitor
  - Zanubrutinib was designed to have greater BTK specificity than ibrutinib[1]
  - Zanubrutinib has exposure coverage above its IC_{50}[2]
  - Higher drug-concentration/IC_{50} ratios would be expected to lead to more sustained and complete BTK inhibition to improve efficacy[2]
- Zanubrutinib has demonstrated superior PFS by IRC over chemoimmunotherapy in treatment-naive CLL/SLL patients without del(17p)[3]

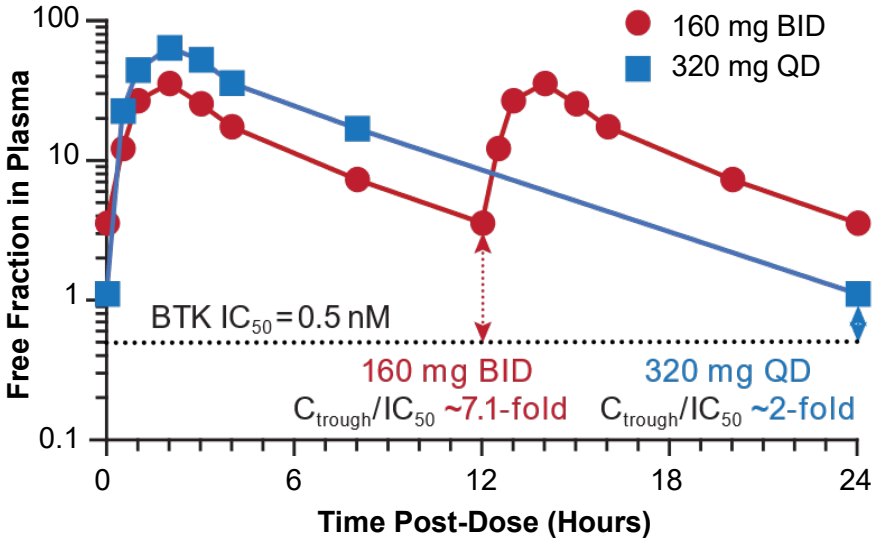
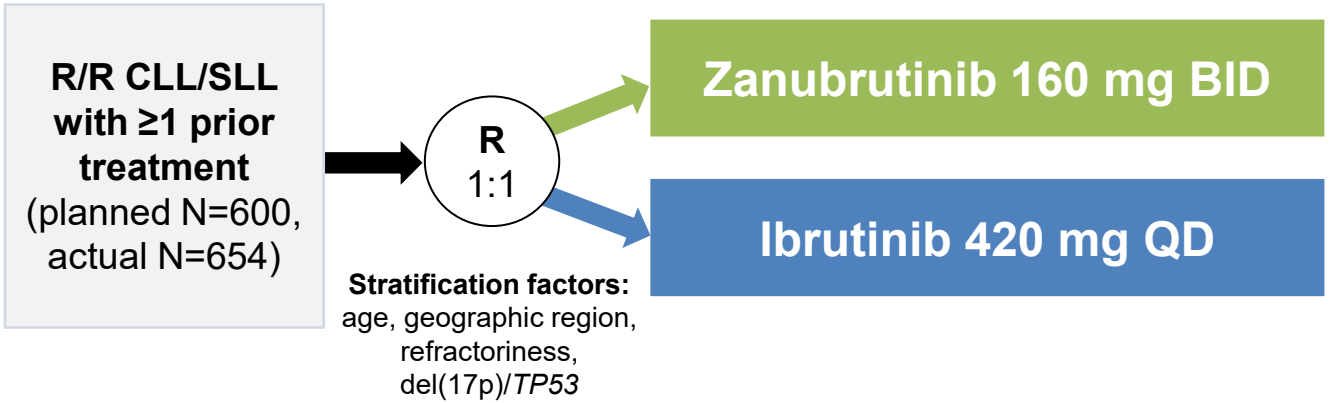


Figure modified from Ou YC, Tang Z, Novotny W, et al. *Leukemia & Lymphoma.* 2021; 62(11):2612-2624.

[1]Guo Y, Liu Y, Hu N, et al.*J Med Chem.* 2019;62(17):7923-7940. [2]Ou YC, Tang Z, Novotny W, et al *Leukemia & Lymphoma.* 2021; 62(11):2612-2624.
[3]Tam CS, Brown JB, Kahl BS, et al. *Lancet Oncol.* 2022; 23(8):1031-1043.

ALPINE Study Design



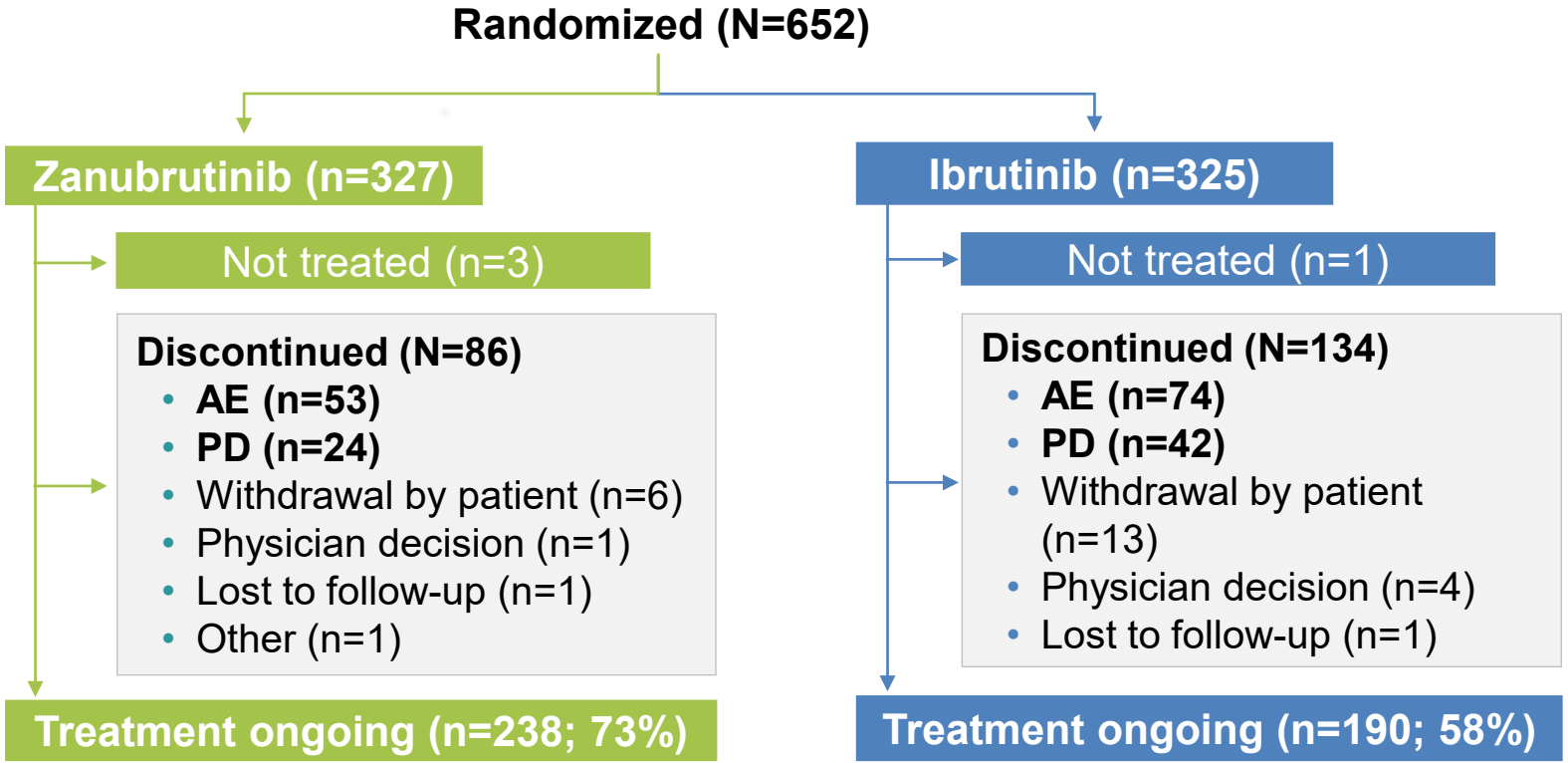
Key Inclusion Criteria
- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI

Key Exclusion Criteria
- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists

Primary Endpoint: ORR (PR+CR) noninferiority and superiority (by investigator)
Key Secondary Endpoints: PFS and incidence of atrial fibrillation
Other Secondary Endpoints: DoR, OS, time to treatment failure, PR-L or higher, PROs, and safety

Hillmen P, Eichhorst E, Brown JR, et al. *J Clin Oncol.* 2023;41(5):1035-104.
CT, computerized tomography; MRI, magnetic resonance imaging; R, randomized.

Patient Disposition



Brown JR, Eichhorst E, Hillmen P, et al. *N Engl J Med.* 2023;388(4):319-332.
AE, adverse event; PD, progressive disease.

Balanced Demographics and Disease Characteristics

	Zanubrutinib (n=327)	Ibrutinib (n=325)
Age, median (range)	**67 (35-90)**	**68 (35-89)**
≥65 years, n (%)	201 (61.5)	200 (61.5)
Male, n (%)	**213 (65.1)**	**232 (71.4)**
ECOG PS ≥1, n (%)	**198 (60.6)**	**203 (62.5)**
Prior lines of systemic therapy, median (range)	**1 (1-6)**	**1 (1-12)**
>3 prior lines, n (%)	24 (7.3)	30 (9.2)
del(17p) and/or *TP53*^{mut}, n (%)	**75 (22.9)**	**75 (23.1)**
del(17p)	45 (13.8)	50 (15.4)
TP53^{mut} without del(17p)	30 (9.2)	25 (7.7)
del(11q), n (%)	**91 (27.8)**	**88 (27.1)**
IGHV mutational status, n (%)		
Mutated	79 (24.2)	70 (21.5)
Unmutated	239 (73.1)	239 (73.5)
Complex karyotype[a]	**56 (17.1)**	**70 (21.5)**
Bulky disease (≥5 cm), n (%)	**145 (44.3)**	**149 (45.8)**

[a]Complex karyotype is defined as having ≥3 abnormalities.

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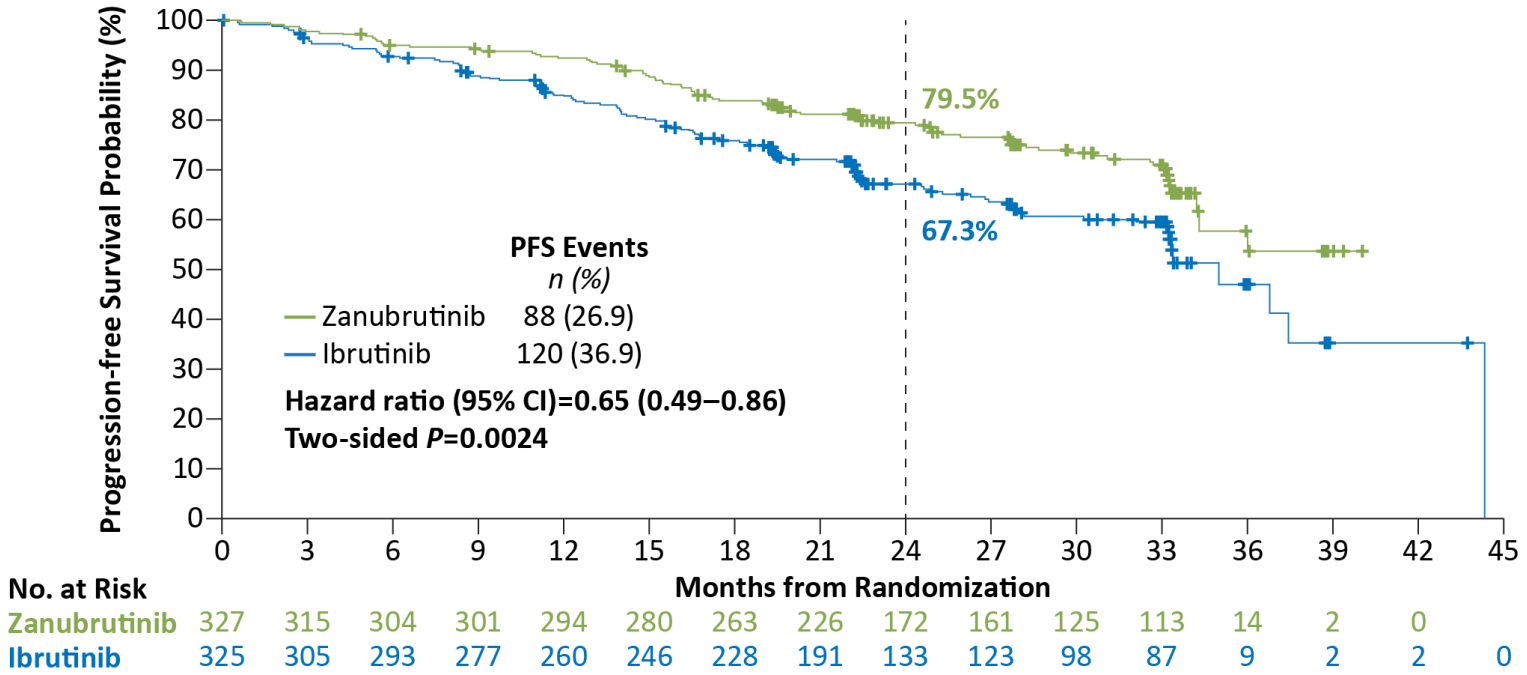
Zanubrutinib PFS Significantly Superior to Ibrutinib

Median study follow-up of 29.6 months



Data cutoff: 8 Aug 2022.
PFS data assessed by IRC.
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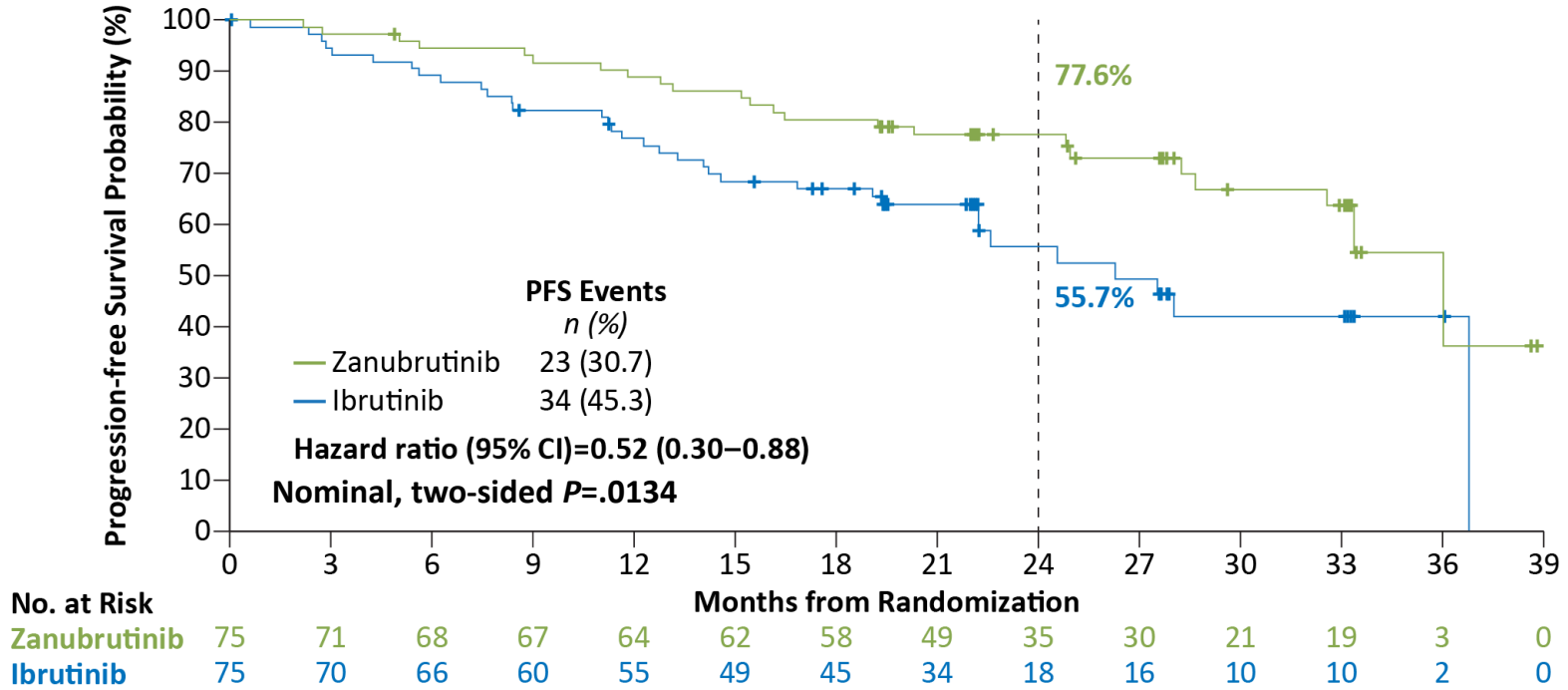
Zanubrutinib Improved PFS in Patients with del(17p)/*TP53*^{mut}



Data cutoff: 8 Aug 2022.
PFS data assessed by IRC.
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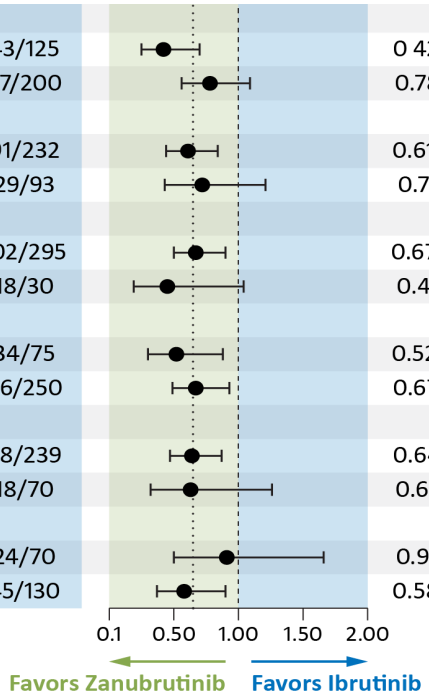
PFS Favored Zanubrutinib Across Subgroups

Subgroup	Zanubrutinib	Ibrutinib	Hazard Ratio (95% CI)[a]
	Events/Patients		ITT: 0.65
Age group			
<65 years	23/126	43/125	0 42 (0.25, 0.70)
≥65 years	65/201	77/200	0.78 (0.56, 1.09)
Sex			
Male	59/213	91/232	0.61 (0.44, 0.84)
Female	29/114	29/93	0.72 (0.43, 1.21)
Prior lines of therapy			
1–3	80/303	102/295	0.67 (0.50, 0.90)
>3	8/24	18/30	0.45 (0.19, 1.04)
Baseline *del*(17p)/*TP53* mutation status			
Present	23/75	34/75	0.52 (0.30, 0.88)
Absent	65/251	86/250	0.67 (0.49, 0.93)
Baseline IGHV mutation status			
Unmutated	72/239	98/239	0.64 (0.47, 0.87)
Mutated	15/79	18/70	0.63 (0.32, 1.26)
Complex karyotype			
Yes	20/56	24/70	0.91 (0.50, 1.66)
No	37/153	45/130	0.58 (0.37, 0.90)



Data cutoff: 8 Aug 2022.

[a]Hazard ratio and 95% CI were unstratified for subgroups.

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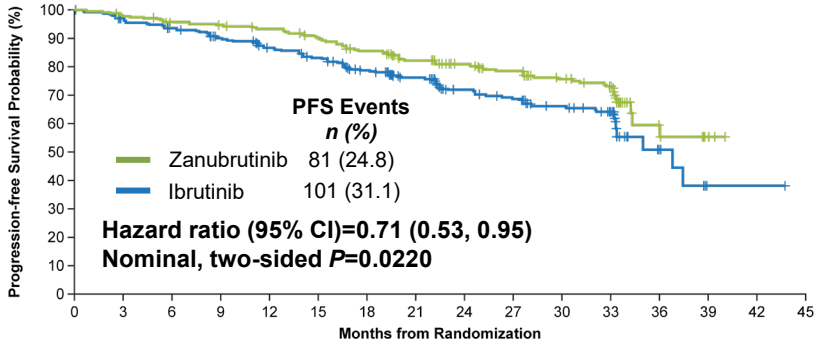
Sensitivity Analyses Are Consistent with Primary PFS Analysis, Including Drug Interruptions and Treatment Discontinuation

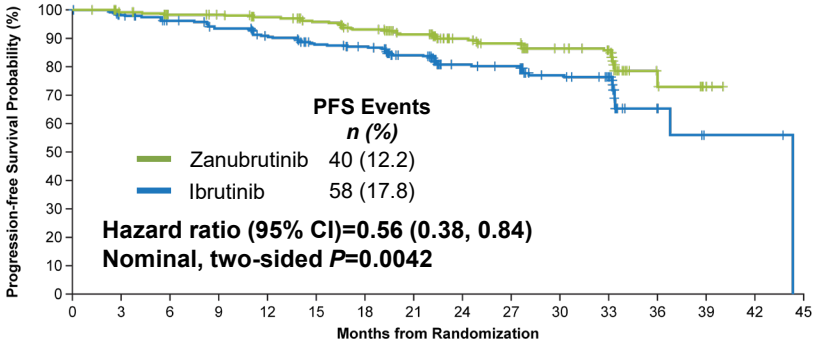
Drug Interruptions[1,2]



No. of Patients at Risk

Zanubrutinib	327	313	303	299	292	279	264	224	169	159	124	113	14	2	0
Ibrutinib	325	301	289	273	256	244	223	190	132	124	99	88	9	1	1	0

Treatment Discontinuation[2]



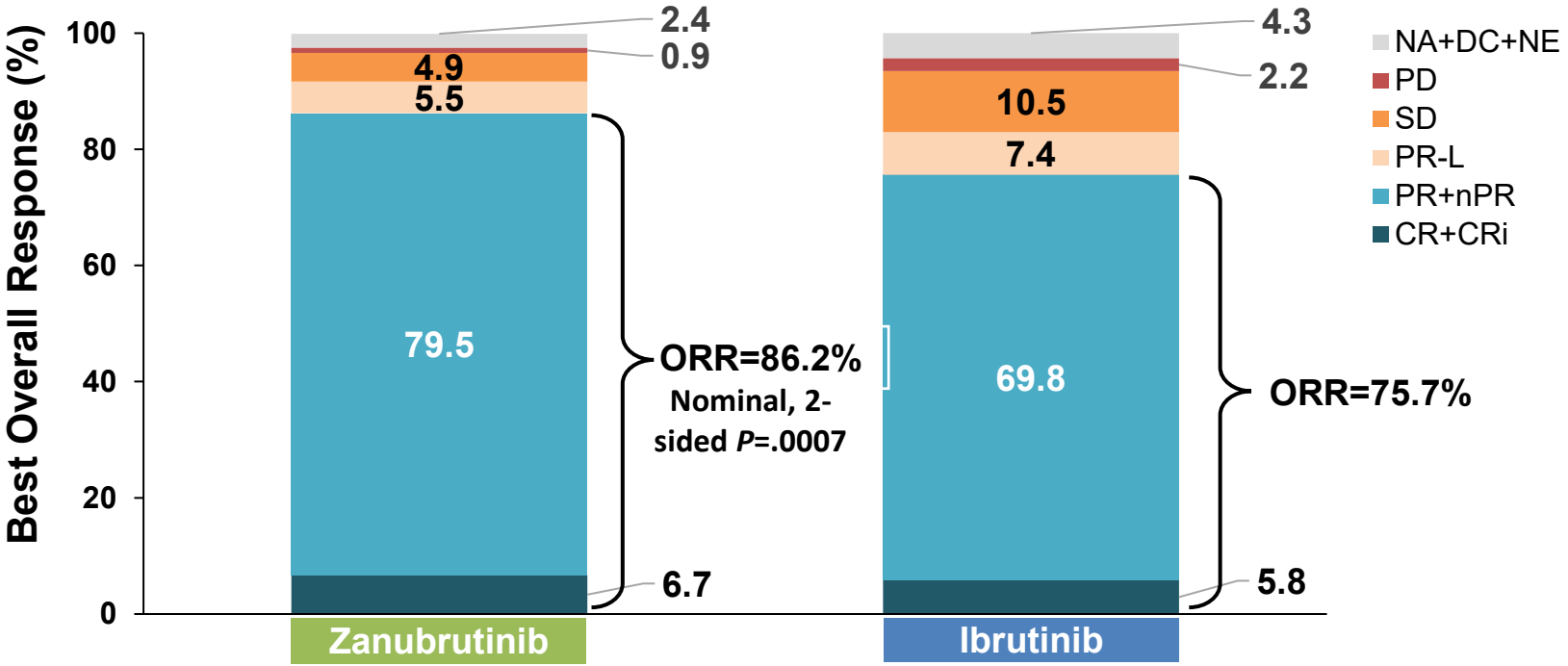
No. of Patients at Risk

Zanubrutinib	327	308	298	294	283	271	258	222	164	156	119	111	14	2	0
Ibrutinib	325	293	275	263	245	225	217	182	122	119	93	85	8	2	2	0

Data cutoff: 8 Aug 2022.

[1]Brown JR, Eichhorst E, Hillmen P, et al. *N Engl J Med.* 2023;388(4):319-332. [2]Data on file.

Zanubrutinib Showed Higher ORR Assessed by IRC



Data cutoff: 8 Aug 2022.

CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable response; PD, progressive disease; NA, not assessed; DC, discontinued prior to first assessment; NE, not evaluable.

Overall Safety/Tolerability Summary

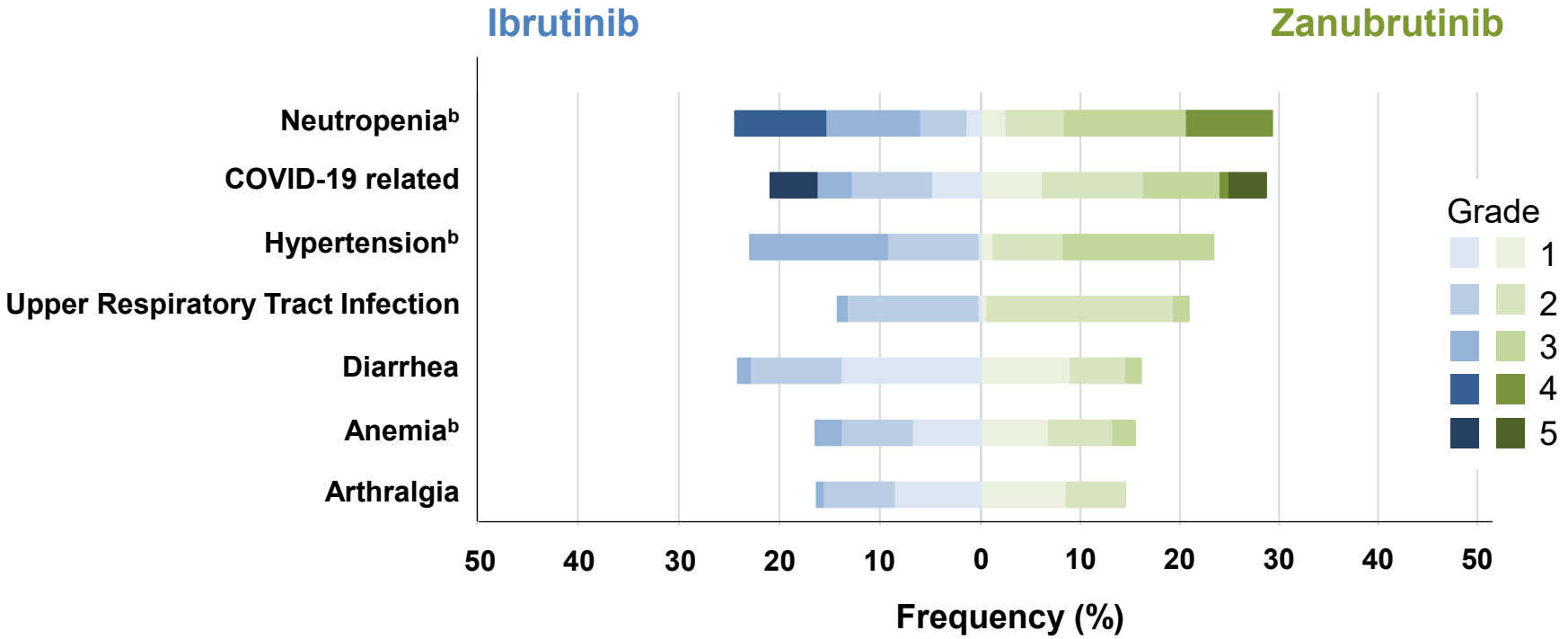
Zanubrutinib safety profile was favorable to ibrutinib

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Median treatment duration, months	**28.4**	**24.3**
Any grade adverse event	**318 (98.1)**	**321 (99.1)**
Grade 3 to 5	218 (67.3)	228 (70.4)
Grade 5	33 (10.2)	36 (11.1)
Serious adverse event	**136 (42.0)**	**162 (50.0)**
Adverse events leading to		
Dose reduction	**40 (12.3)**	**55 (17.0)**
Dose interruption	**162 (50.0)**	**184 (56.8)**
Treatment discontinuation	**50 (15.4)**	**72 (22.2)**

Data cutoff: 8 Aug 2022.

Brown JR, Eichhorst E, Hillmen P, et al. *N Engl J Med.* 2023;388(4):319-332.

Most Common Adverse Events[a]



Data cutoff: 8 Aug 2022.

[a]Adverse events occurring in ≥15% of patients in either arm. [b]Pooled terms.

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Zanubrutinib Had A Favorable Cardiac Profile

Lower rate of cardiac events, serious cardiac events, treatment discontinuation, and deaths

- Lower rate of serious cardiac adverse events reported with zanubrutinib
  - A fib/flutter (n=2)
  - MI/ACS (n=2)
  - CHF (n=2)
- **Fatal cardiac events:**
  - **Zanubrutinib, n=0 (0%)**
  - **Ibrutinib, n=6 (1.9%)**

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac adverse events	**69 (21.3%)**	**96 (29.6%)**
Serious cardiac adverse events	**6 (1.9%)**	**25 (7.7%)**
Cardiac adverse events leading to treatment discontinuation	**1 (0.3)**	**14 (4.3)**
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation	0	5 (1.5)
Cardiac arrest	0	2 (0.6)[a]
Cardiac failure	0	2 (0.6)
Cardiac failure acute	0	1 (0.3)[a]
Congestive cardiomyopathy	0	1 (0.3)[a]
Myocardial infarction	0	1 (0.3)[a]
Palpitations	0	1 (0.3)
Ventricular fibrillation	0	1 (0.3)

[a]Cardiac deaths. One death not listed due to myocardial infarction with ibrutinib discontinuation due to diarrhea 14 days prior to the fatal event.

Data cutoff: 8 Aug 2022

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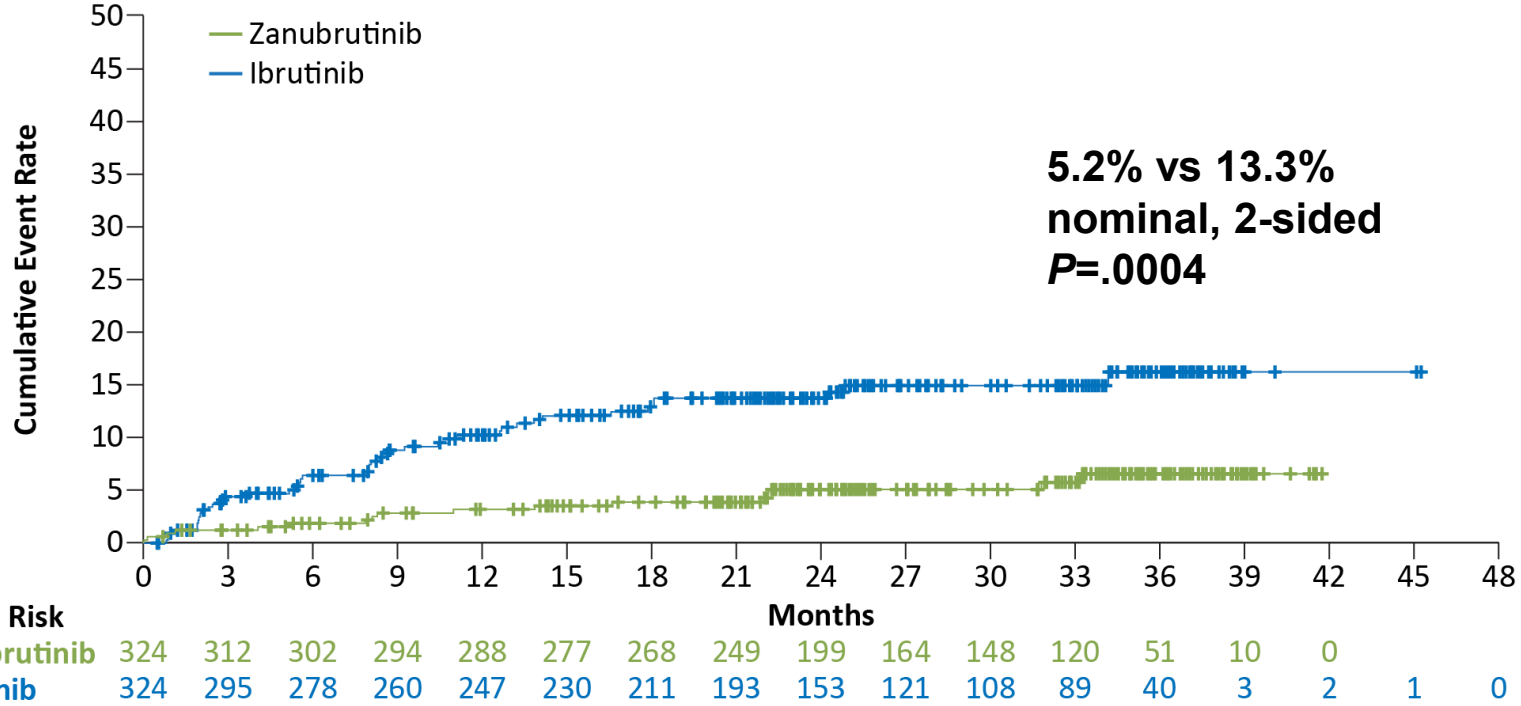
Fewer Atrial Fibrillation/Flutter Events With Zanubrutinib



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Conclusions

- Zanubrutinib demonstrated superior PFS over ibrutinib in patients with relapsed/refractory CLL/SLL
  - PFS benefit seen across all major subgroups, including the del(17p)/*TP53*^{mut} population
- Zanubrutinib has a favorable safety profile compared with ibrutinib
  - Lower rate of grade ≥3 and serious AEs, fewer AEs leading to treatment discontinuation and dose reduction
  - Zanubrutinib has a better cardiac profile than ibrutinib with lower rates of atrial fibrillation, serious cardiac events, cardiac events leading to treatment discontinuation, and fatal cardiac events
- ALPINE is the first study to demonstrate PFS superiority in a head-to-head comparison of BTK inhibitors in patients with relapsed/refractory CLL/SLL; **zanubrutinib has now proven superiority to ibrutinib in both PFS and ORR**

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