Zanubrutinib in Relation to Ibrutinib Improves PFS in Patients With Refractory/Recurrent CLL: Final PFS Analysis of the ALPINE Study

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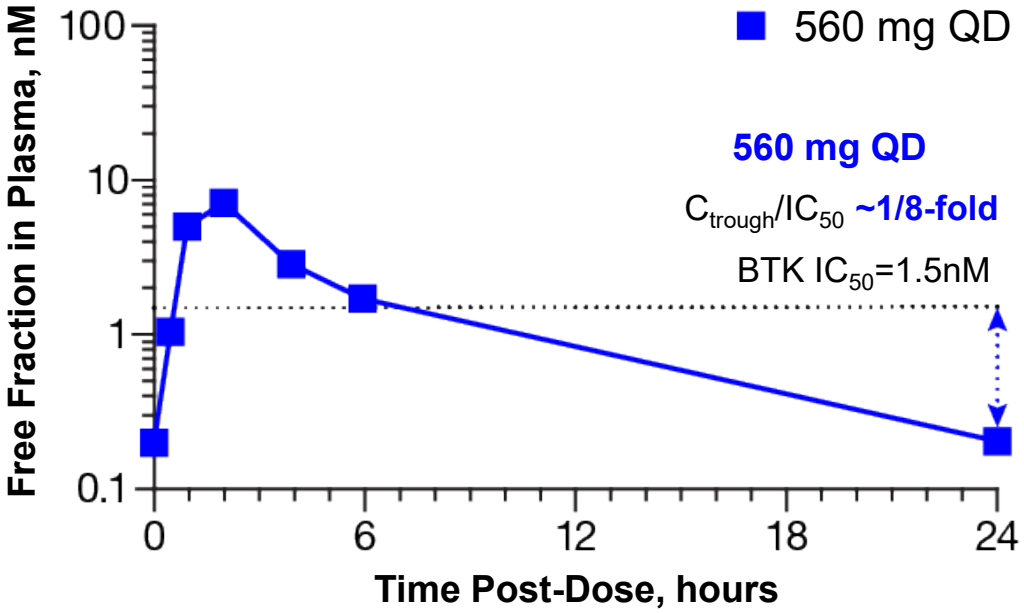
Bruton Tyrosine Kinase Inhibition in CLL: Background

- BCR signaling is required for tumor expansion and proliferation in CLL and B-cell lymphomas[1]
  - BCR signaling is dependent on BTK
- Ibrutinib, a first-in-class, covalent BTK inhibitor, has transformed CLL therapy; however, it has properties that limit use
  - Treatment discontinuation from toxicities has been reported in 16%-23% of patients[2-5]
  - Exposure coverage between dosing intervals falls below IC_{50} and variable BTK occupancy at trough has been observed

Ibrutinib concentration-time profile[6]

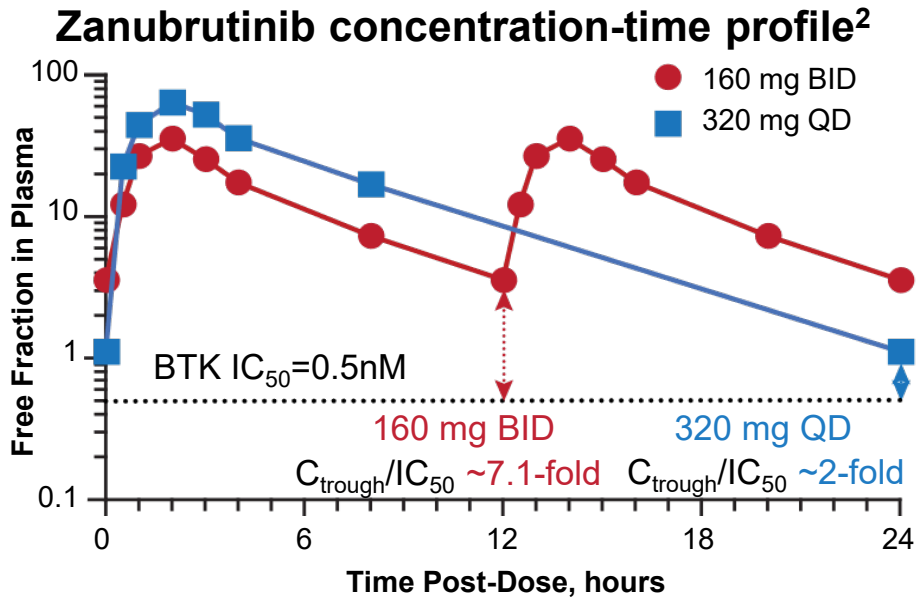


BCR, B-cell antigen receptor; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; C_{trough}, trough concentration; IC_{50}, half maximal inhibitory concentration; QD, daily.

1. Singh SP, et al. Molecular Cancer. 2018; 17:57. 2. Sharman JP, et al. Blood. 2017;130(suppl 1):4060. 3. Mato AR, et al. Haematologica. 2018;103(5):874-879. 4. Munir T, et al. Am J Hematol. 2019;94(12):1353-1363. 5. Ghia P, et al. EHA Abstract EP636 2021. 6. Tam CS et al. Expert Rev Clin Pharmacol. 2021;14:11, 1329-1344.

Zanubrutinib: Differentiating Features and Background

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



BID, twice daily; BTK, Bruton tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; del(17p), deletion in chromosome 17p; IC50, half maximal inhibitory concentration; IRC, independent review committee; PFS, progression-free survival; QD, daily; SLL, small lymphocytic lymphoma.

1. Tam CS, et al. Lancet Oncol. 2022;23(8):1031-1043. 2. Ou YC, et al Leukemia & Lymphoma. 2021; 62(11):2612-2624.

ALPINE Study Design

R/R CLL/SLL with ≥ 1 prior treatment

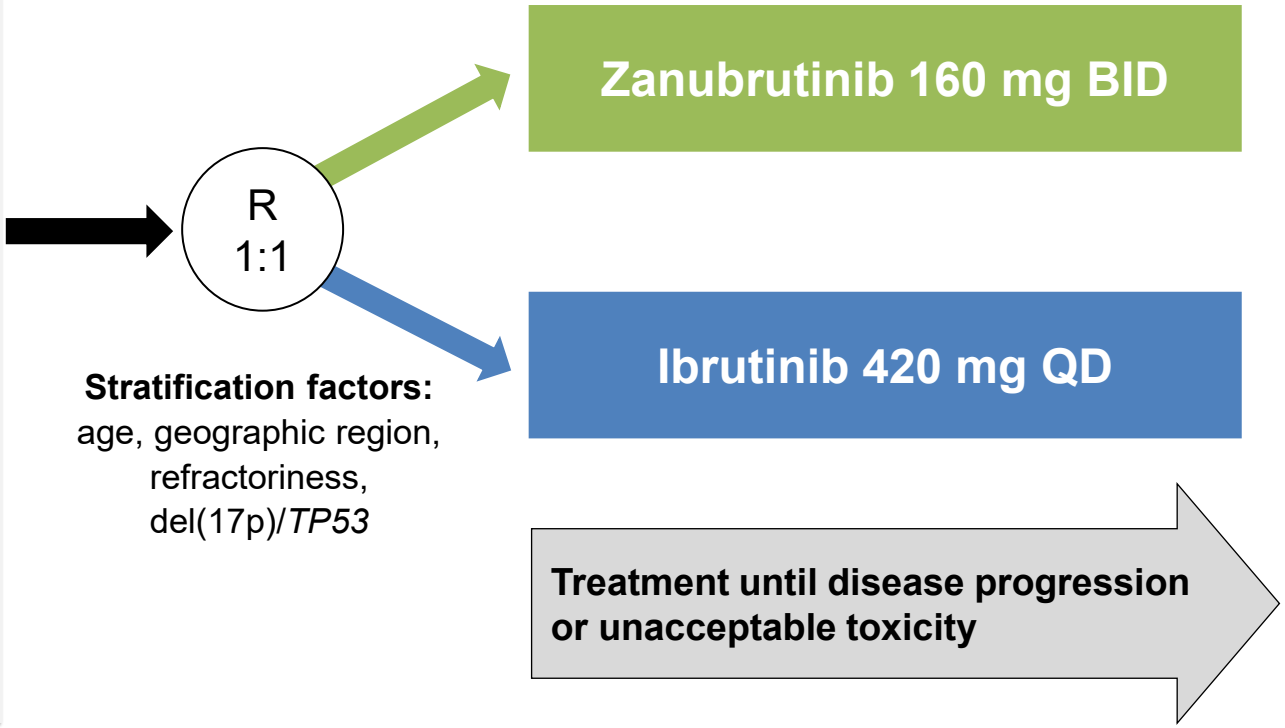
(Planned N=600, Actual N=652)

Key Inclusion Criteria

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

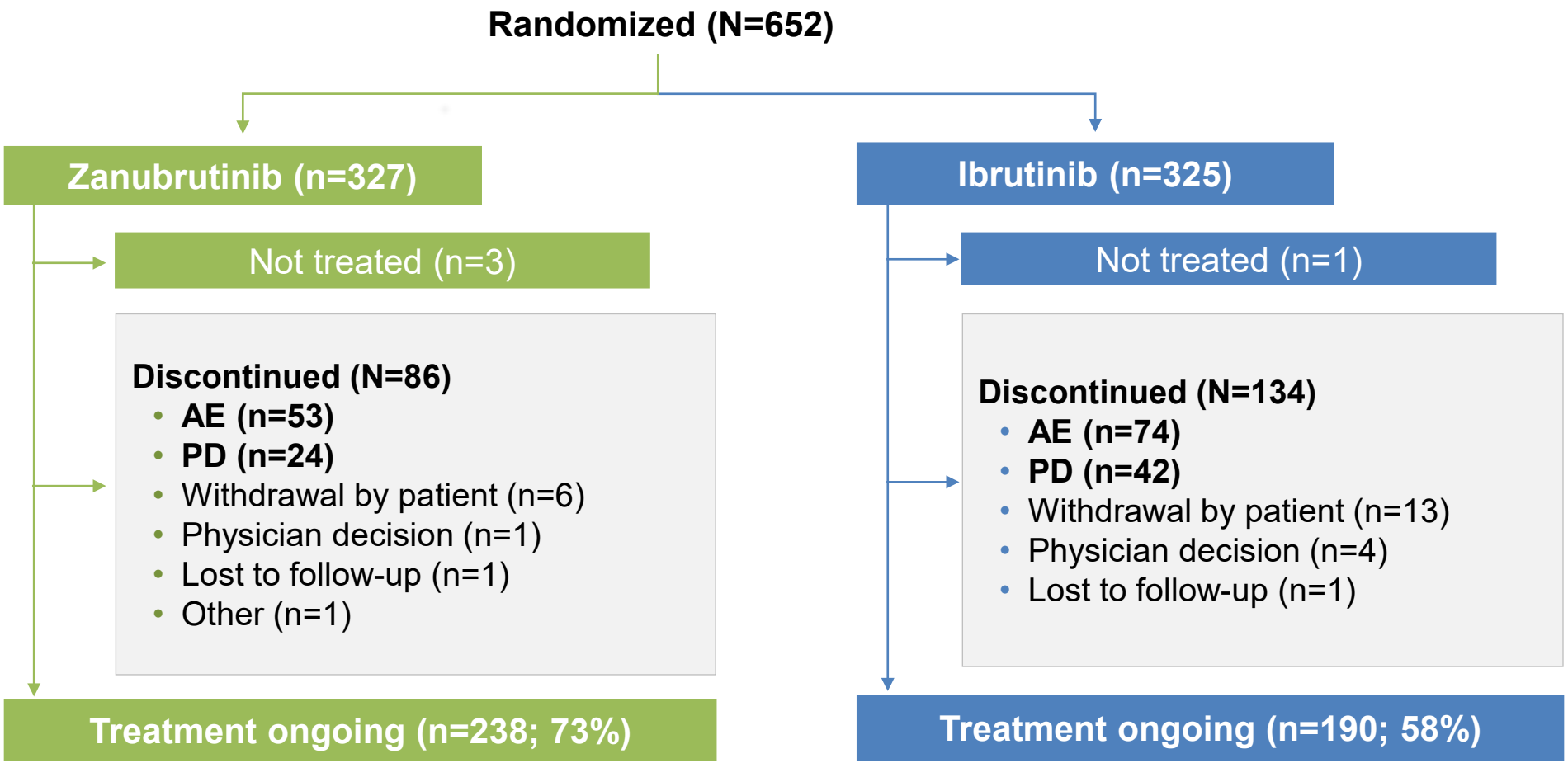
Key Exclusion Criteria

- Prior BTKi therapy
- Treatment with warfarin or other vitamin K antagonists



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

Patient Disposition



AE, adverse event; PD, progressive disease.

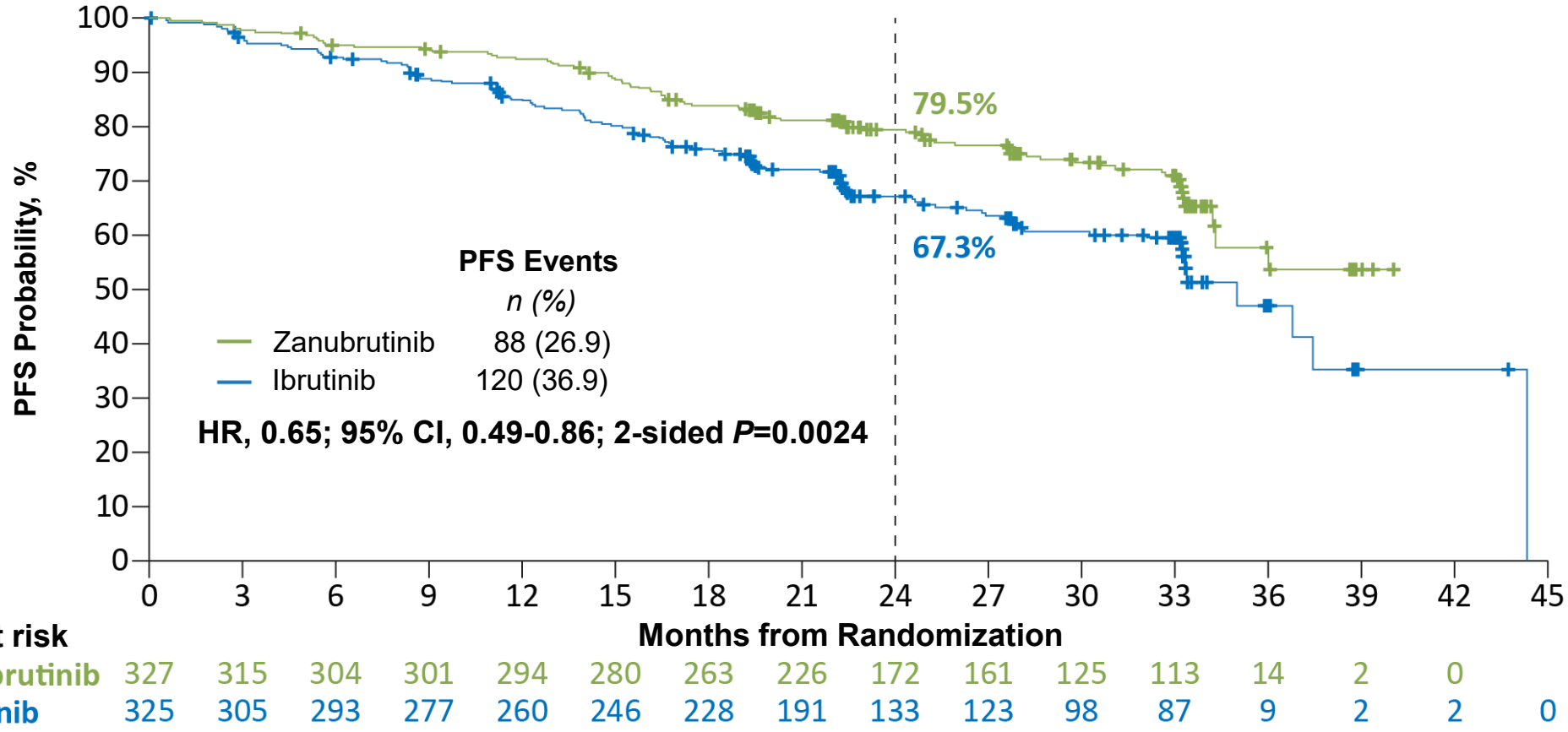
Balanced Demographics and Disease Characteristics

	Zanubrutinib (n=327)	Ibrutinib (n=325)
Age, median (range) ≥65 years, n (%)	**67 (35-90)** 201 (61.5)	**68 (35-89)** 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) >3 prior lines, n (%)	**1 (1-6)** 24 (7.3)	**1 (1-12)** 30 (9.2)
del(17p) and/or *TP53*^{mut}, n (%) del(17p) *TP53*^{mut} without del(17p)	**75 (22.9)** 45 (13.8) 30 (9.2)	**75 (23.1)** 50 (15.4) 25 (7.7)
del(11q), n (%)	**91 (27.8)**	**88 (27.1)**
IGHV mutational status, n (%) Mutated **Unmutated**	 79 (24.2) **239 (73.1)**	 70 (21.5) **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.
ECOG PS, Eastern Cooperative Oncology Group performance status; del(11q), deletion in chromosome 11q; del(17p), deletion in chromosome 17p; IGHV, immunoglobulin heavy chain variable region; *TP53*^{mut}, tumor protein 53 mutation.

Zanubrutinib PFS by IRC Superior to Ibrutinib

- Median study follow-up of 29.6 months

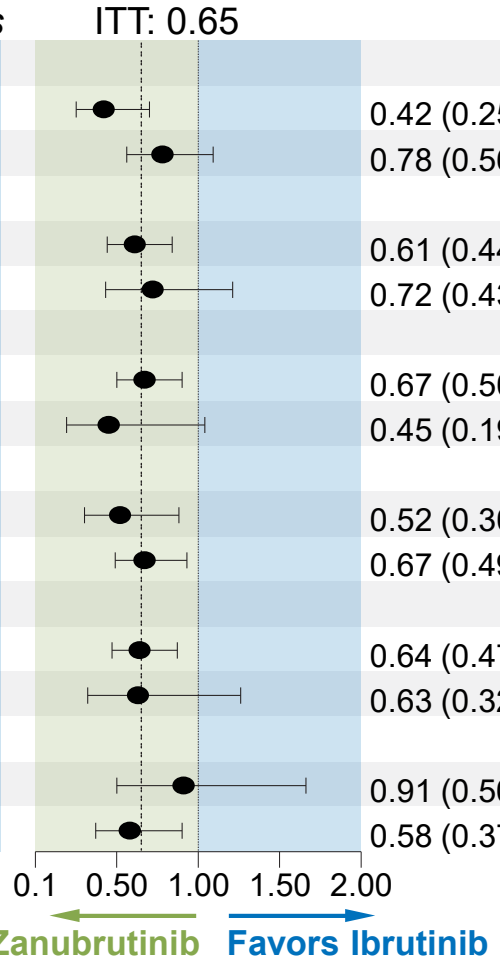


DCO, data cutoff; HR, hazard ratio; PFS, progression-free survival.

DCO: 8 Aug 2022

PFS Favored Zanubrutinib Across Subgroups

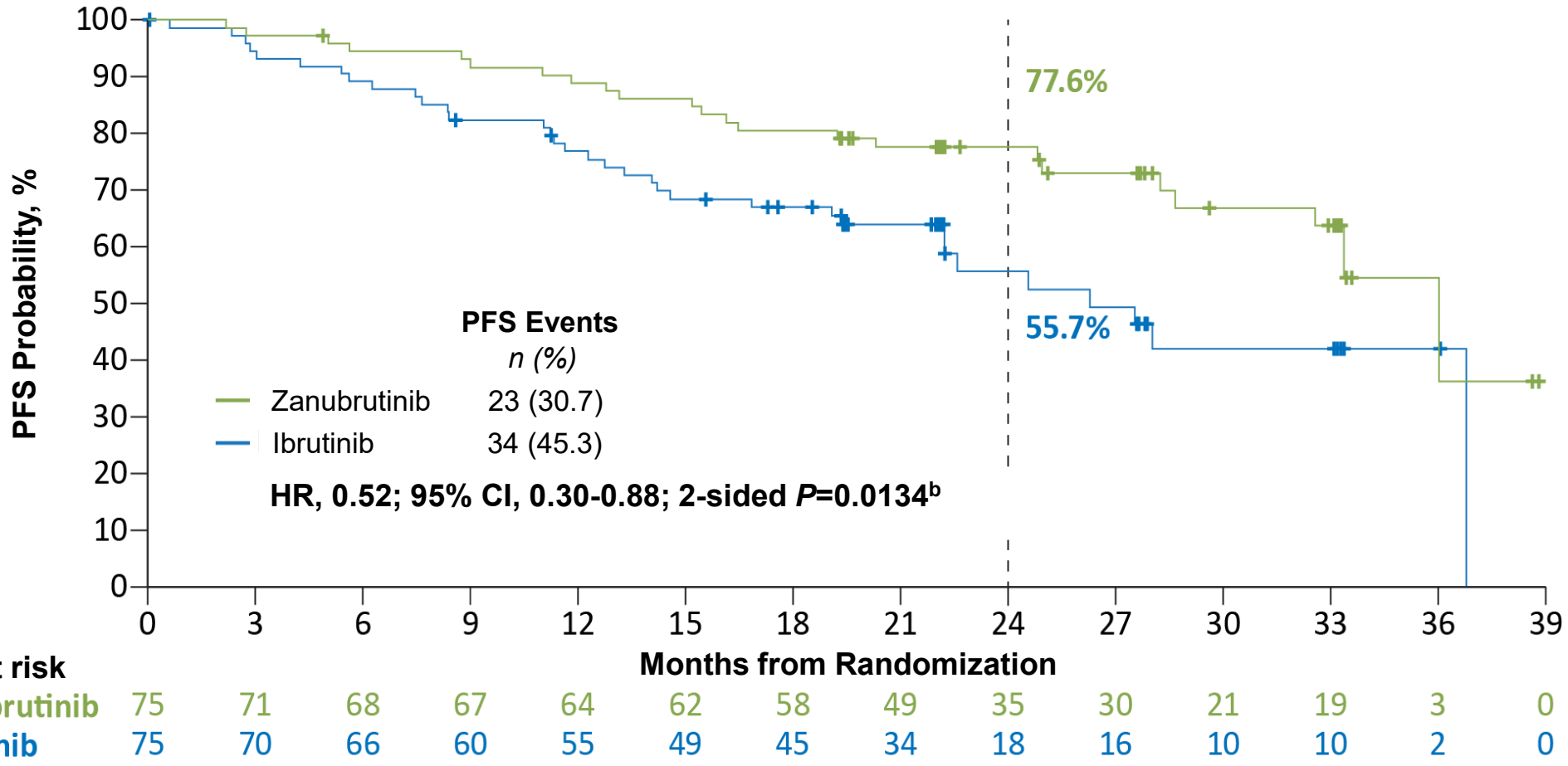
Subgroup	Zanubrutinib *Response/Patients*	Ibrutinib *Response/Patients*	HR (95% CI)[a]
Age group			
<65 years	23/126	43/125	0.42 (0.25-0.70)
≥65 years	65/201	77/200	0.78 (0.56-1.09)
Sex			
Male	59/213	91/232	0.61 (0.44-0.84)
Female	29/114	29/93	0.72 (0.43-1.21)
Prior lines of therapy			
1-3	80/303	102/295	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 mutational 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)



[a] HR and 95% CI were unstratified for subgroups.
DCO, data cutoff; del(17p), deletion in chromosome 17p; HR, hazard ratio; IGHV, immunoglobulin heavy chain variable region; ITT, intention to treat; *TP53*, tumor protein 53.

DCO: 8 Aug 2022

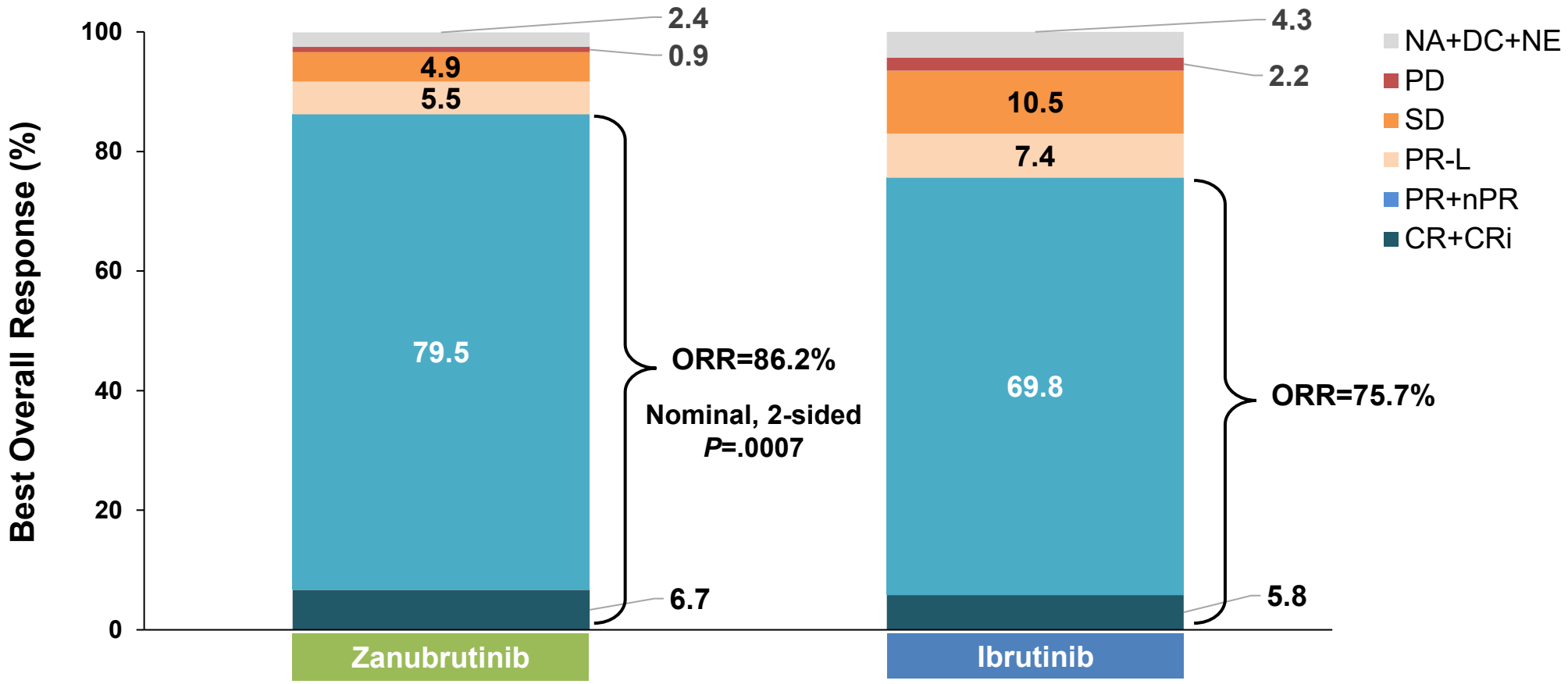
Zanubrutinib Improved PFS[a] in Patients with del(17p)/*TP53*^{mut}



[a] PFS data assessed by IRC. [b] Nominal *P* value.
del(17p), deletion in chromosome 17p; DCO, data cutoff; HR, hazard ratio; PFS, progression-free survival; *TP53*^{mut}, tumor protein 53 mutation.

DCO: 8 Aug 2022

Zanubrutinib Showed Higher ORR Assessed by IRC



DCO: 8 Aug 2022

CR, complete response; CRi, complete response with incomplete bone marrow recovery; DC, discontinued prior to first assessment; DCO, data cutoff; IRC, independent review committee; NA, not assessed; NE, not evaluable; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

Overall Safety/Tolerability Summary

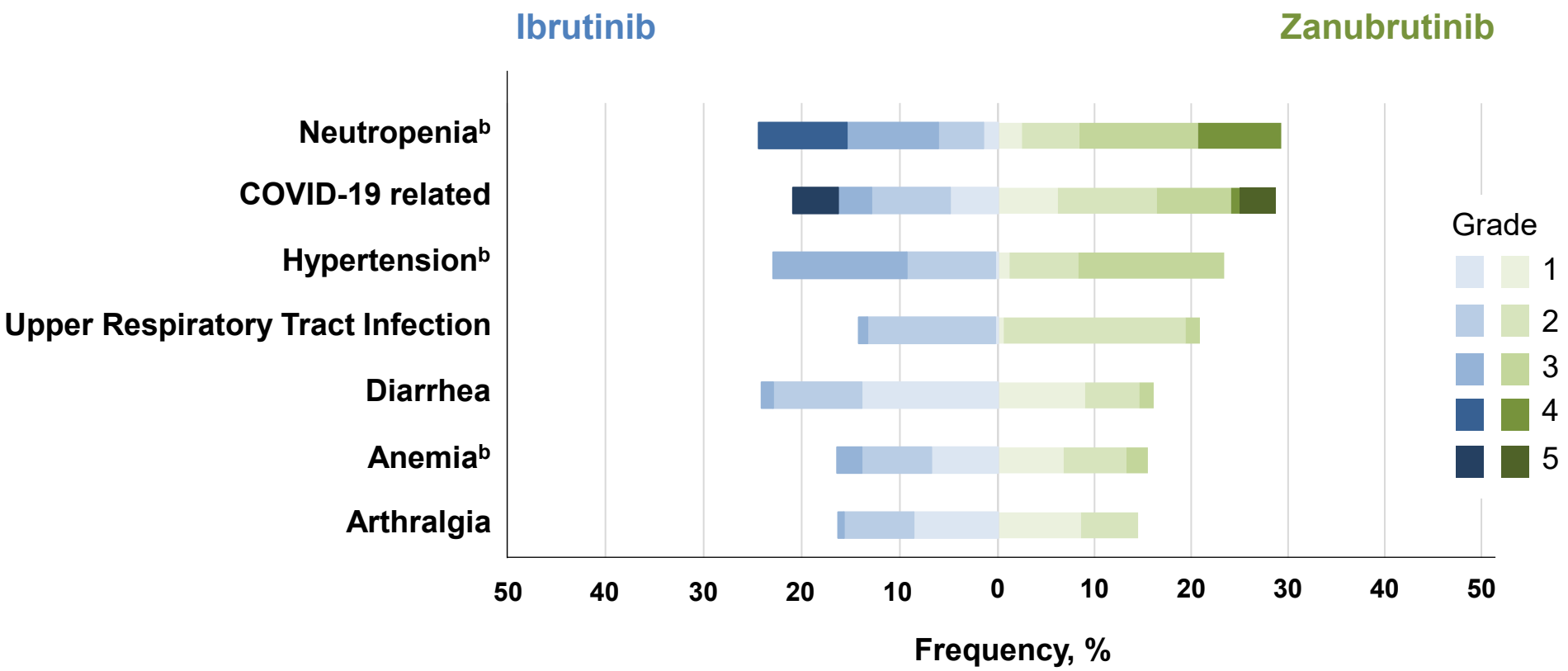
- **Zanubrutinib safety profile was more favorable compared with ibrutinib**

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Median treatment duration, months	**28.4**	**24.3**
Any grade AE	**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 AE	**136 (42.0)**	**162 (50.0)**
AEs 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)**

AE, adverse event; DCO, data cutoff.

DCO: 8 Aug 2022

Most Common Adverse Events[a]



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

DCO: 8 Aug 2022

Zanubrutinib had a Favorable Cardiac Profile

- Lower rates of cardiac events, serious cardiac events, treatment discontinuation, and deaths

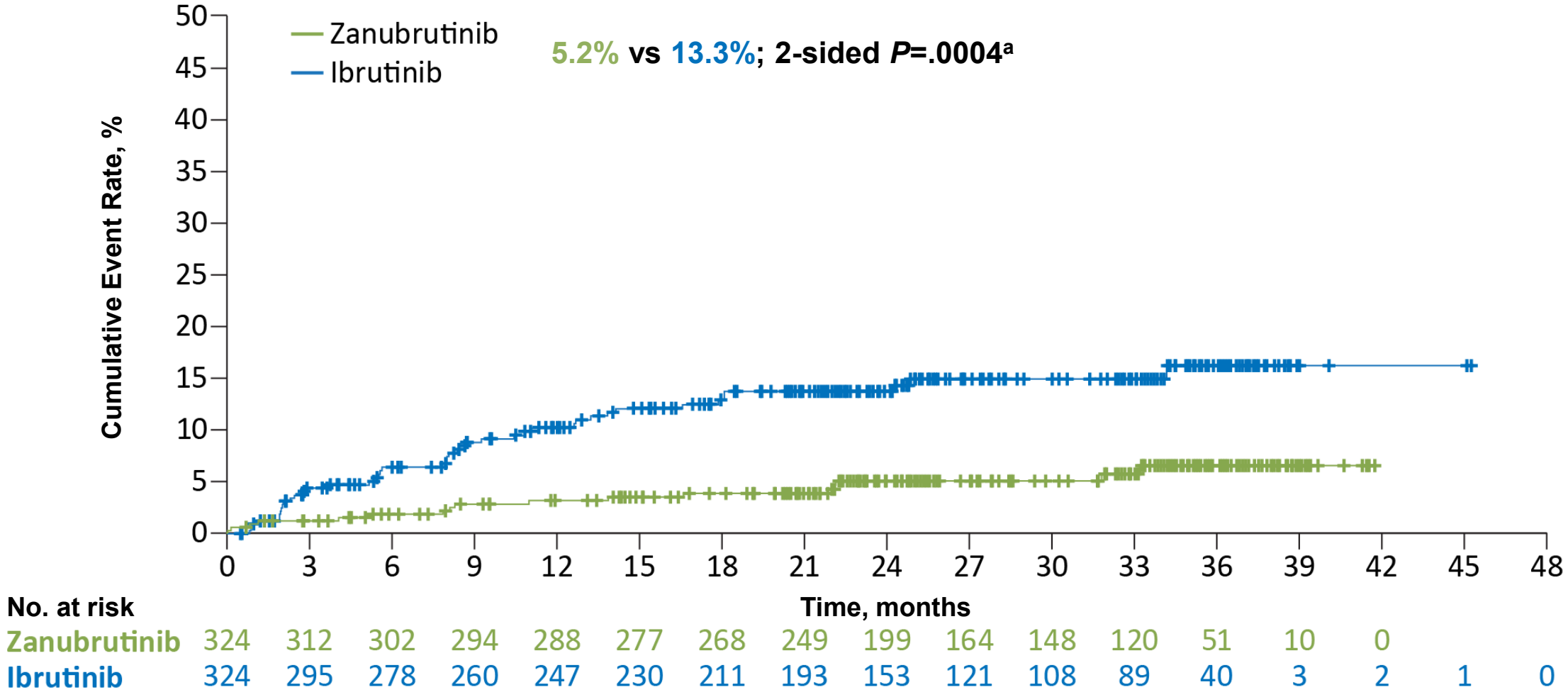
- Lower rate of serious cardiac AEs reported with zanubrutinib
  - Atrial fibrillation/flutter (n=2)
  - MI/ACS (n=2)
  - CHF (n=2)
- **Fatal cardiac events:**
  - **Zanubrutinib, n=0 (0%)**
  - **Ibrutinib, n=6 (1.9%)**

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac AEs	**69 (21.3%)**	**96 (29.6%)**
Serious cardiac AEs	**6 (1.9%)**	**25 (7.7%)**
Cardiac AEs 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.
ACS, acute coronary syndrome; AE, adverse event; CHF, congestive heart failure; DCO, data cutoff; MI, myocardial infarction.

DCO: 8 Aug 2022

Fewer Atrial Fibrillation/Flutter Events With Zanubrutinib



[a] Nominal *P* value.
DCO, data cutoff.

DCO: 8 Aug 2022

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 had 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 had 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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