Zanubrutinib Demonstrated Superior Progression-Free Survival vs Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: Final PFS Analysis of Phase 3 ALPINE Study

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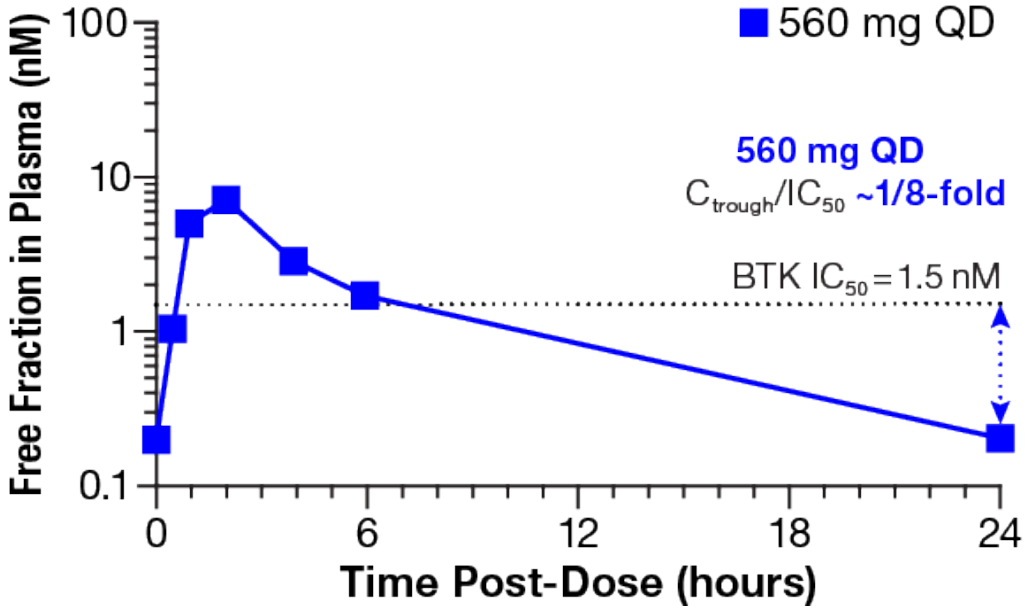
Bruton Tyrosine Kinase Inhibition in CLL: Background

- 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.

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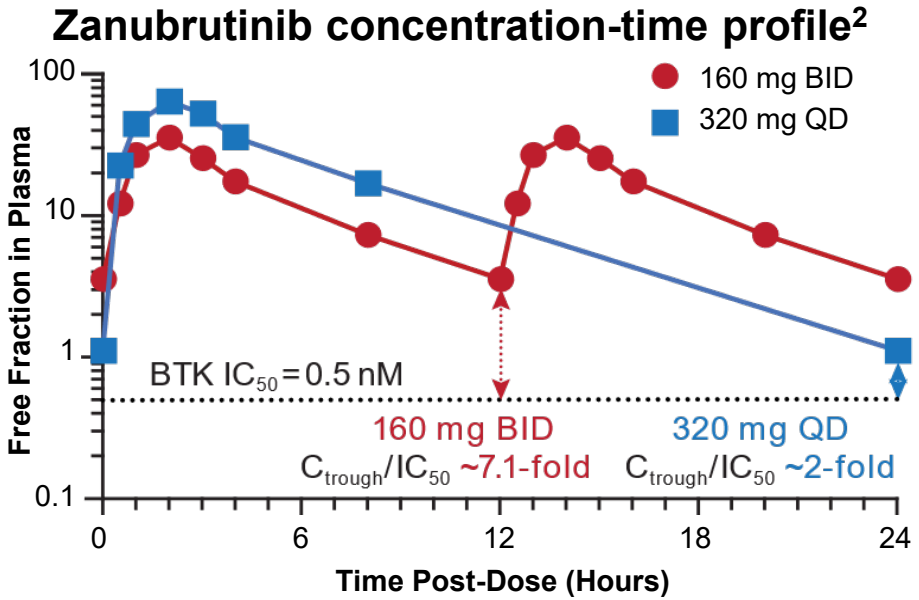
Zanubrutinib: Differentiating Features and Background

- 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.

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ALPINE Study Design

R/R CLL/SLL with ≥ 1 prior treatment

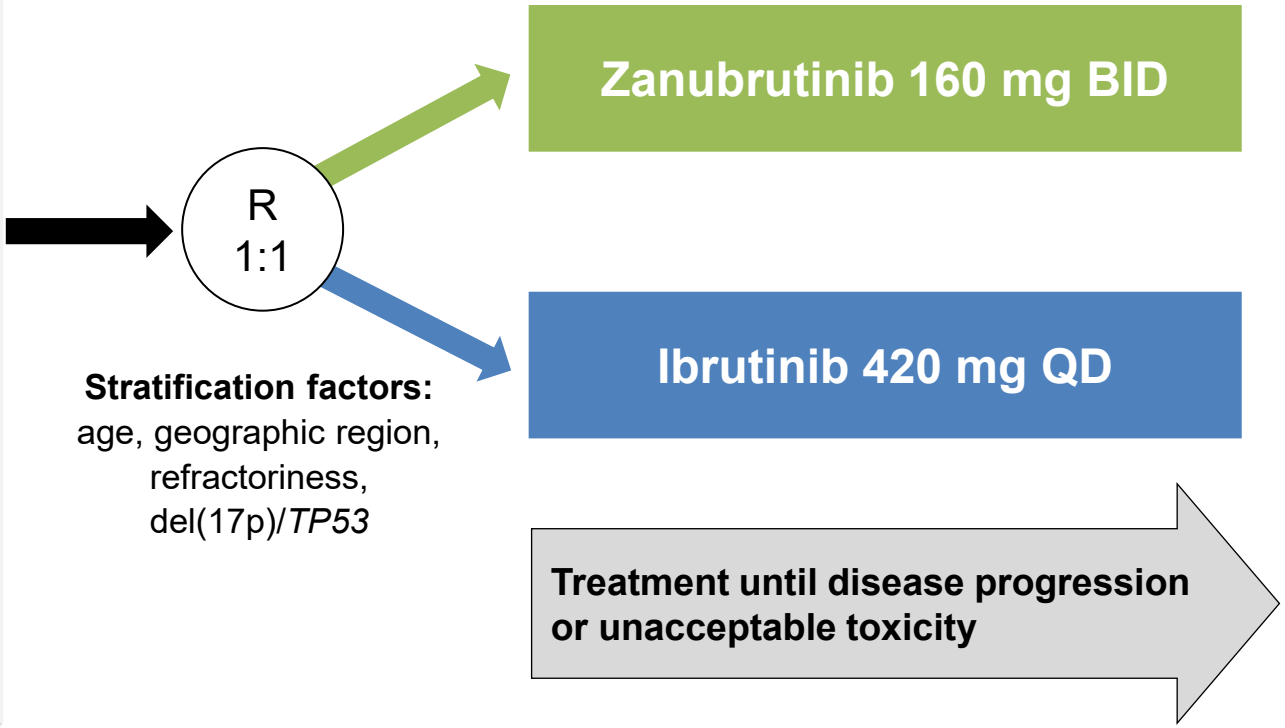
(Planned N=600, Actual N=652)

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.

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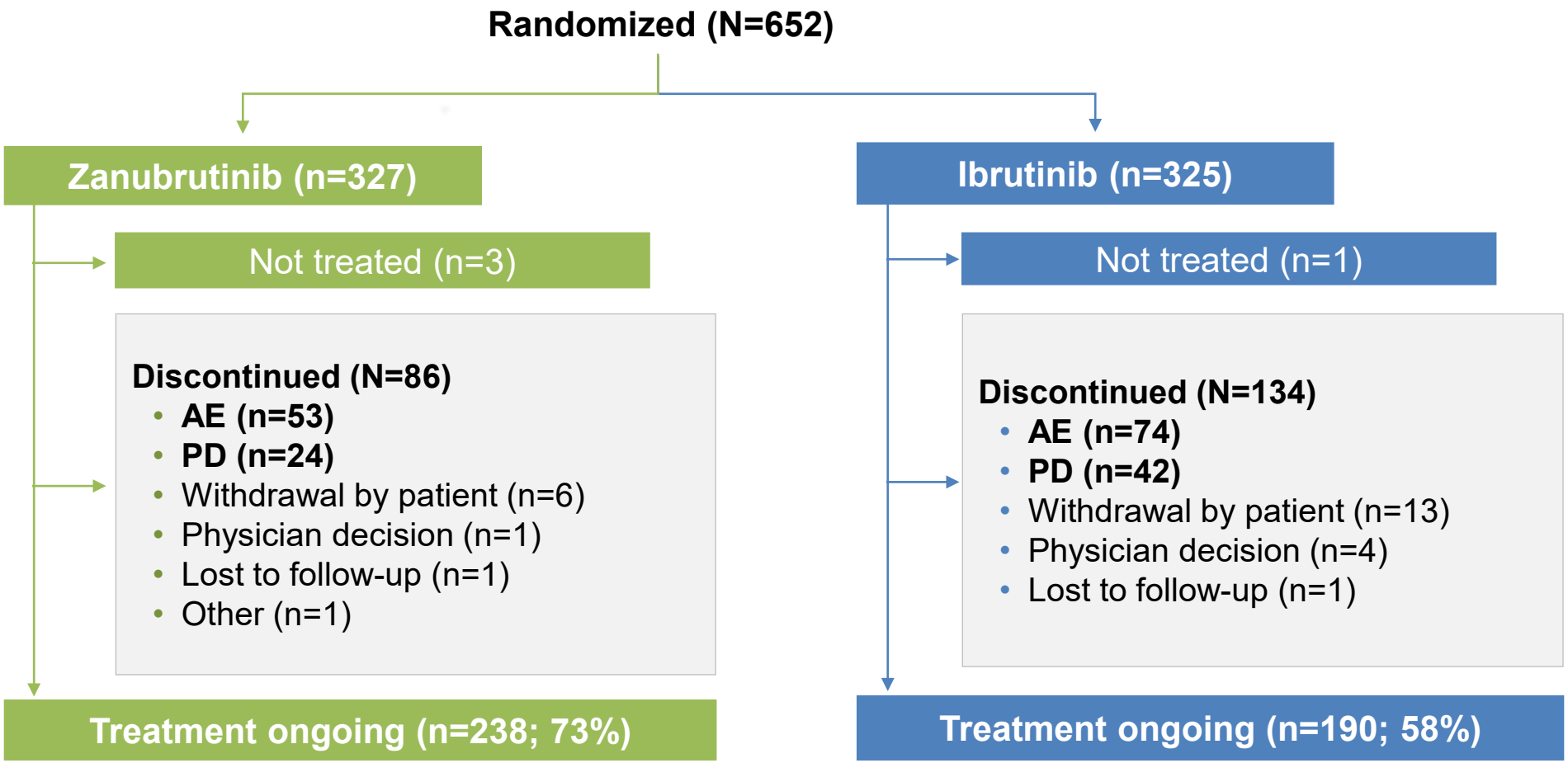
Patient Disposition



AE, adverse event; PD, progressive disease.

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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.

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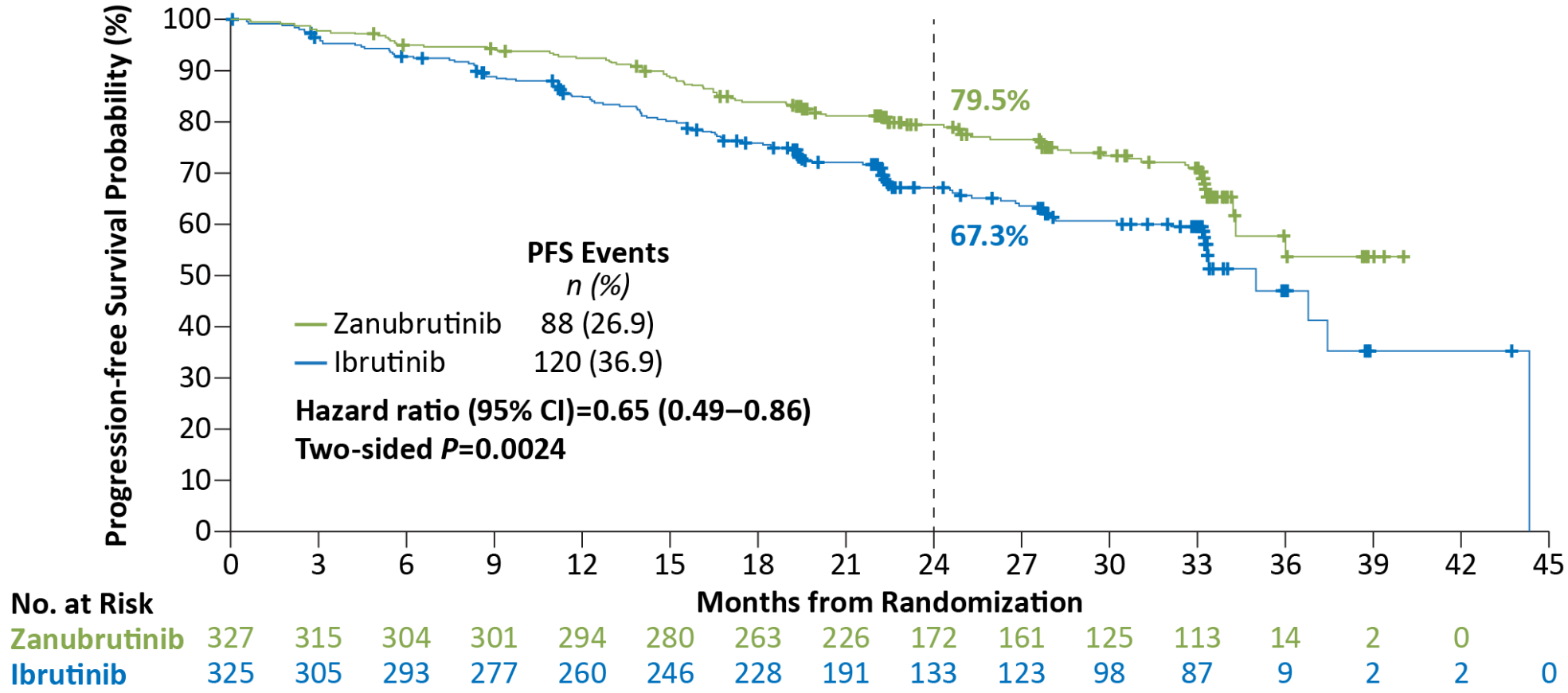
Zanubrutinib PFS by IRC Superior to Ibrutinib

- Median study follow-up of 29.6 months



CI, confidence interval; DCO, data cutoff; PFS, progression-free survival.

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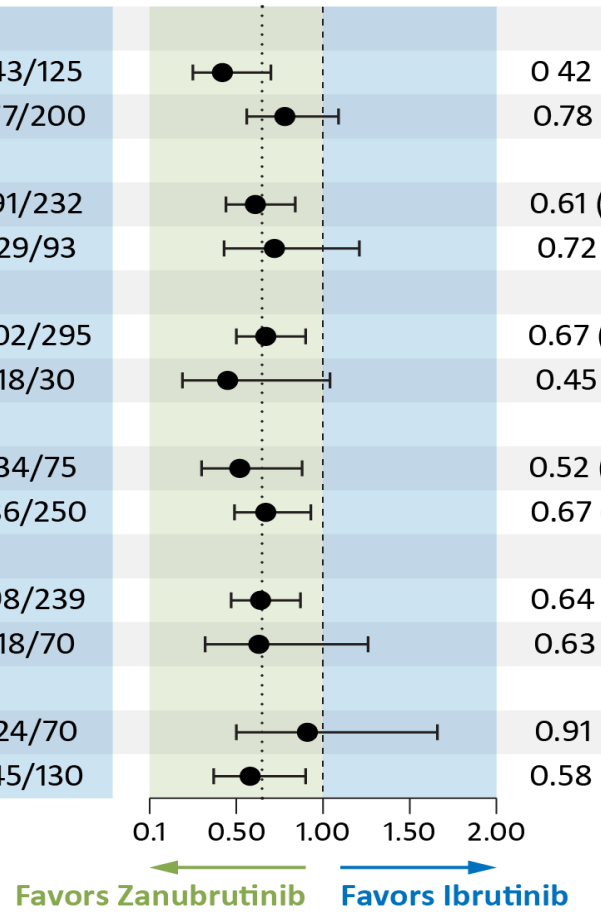
PFS Favored Zanubrutinib Across Subgroups

Subgroup	Zanubrutinib Response/Patients	Ibrutinib Response/Patients	Hazard Ratio (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 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)



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

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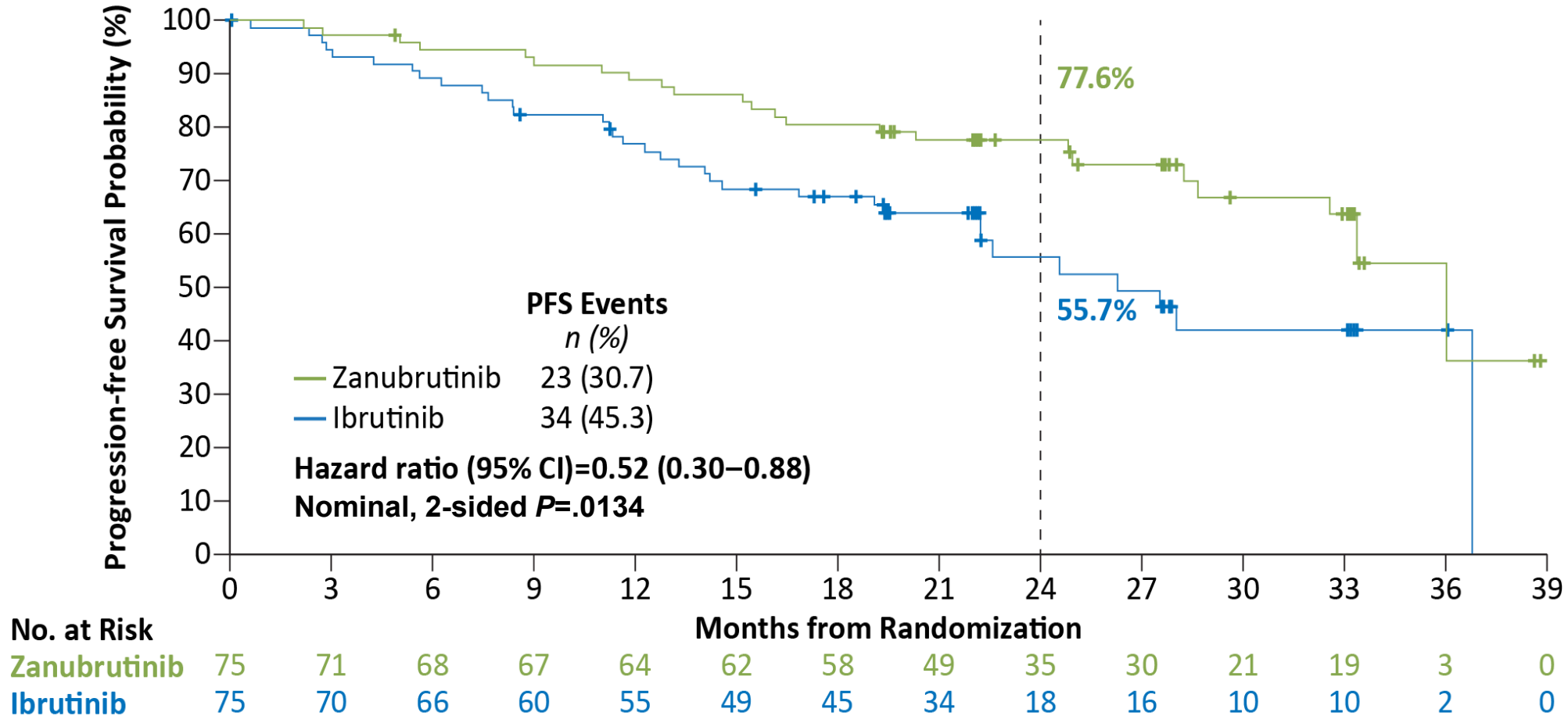
Zanubrutinib Improved PFS[a] in Patients with del(17p)/*TP53*^{mut}



[a] PFS data assessed by IRC.
CI, confidence interval; del(17p), deletion in chromosome 17p; DCO, data cutoff; PFS, progression-free survival; *TP53*^{mut}, tumor protein 53 mutation.

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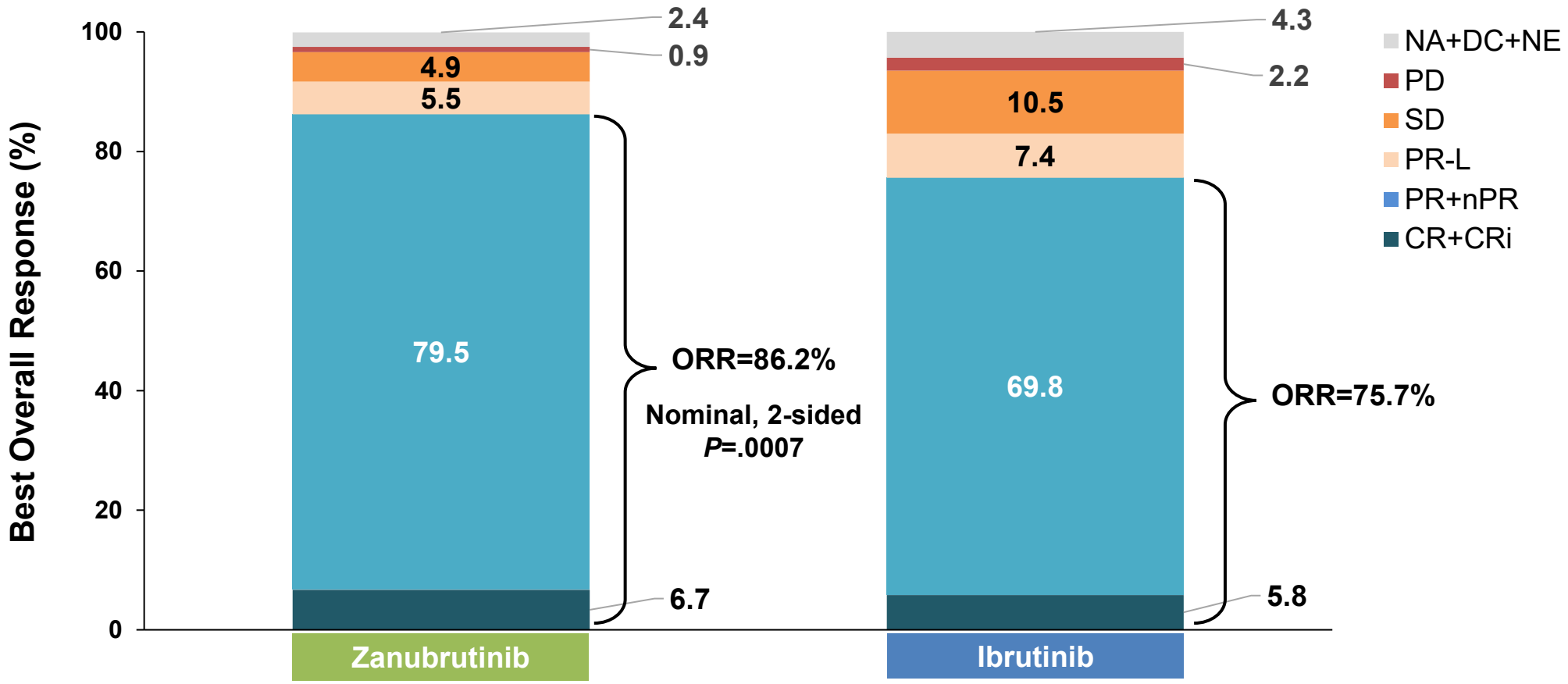
Zanubrutinib Showed Higher ORR Assessed by IRC



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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.

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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.

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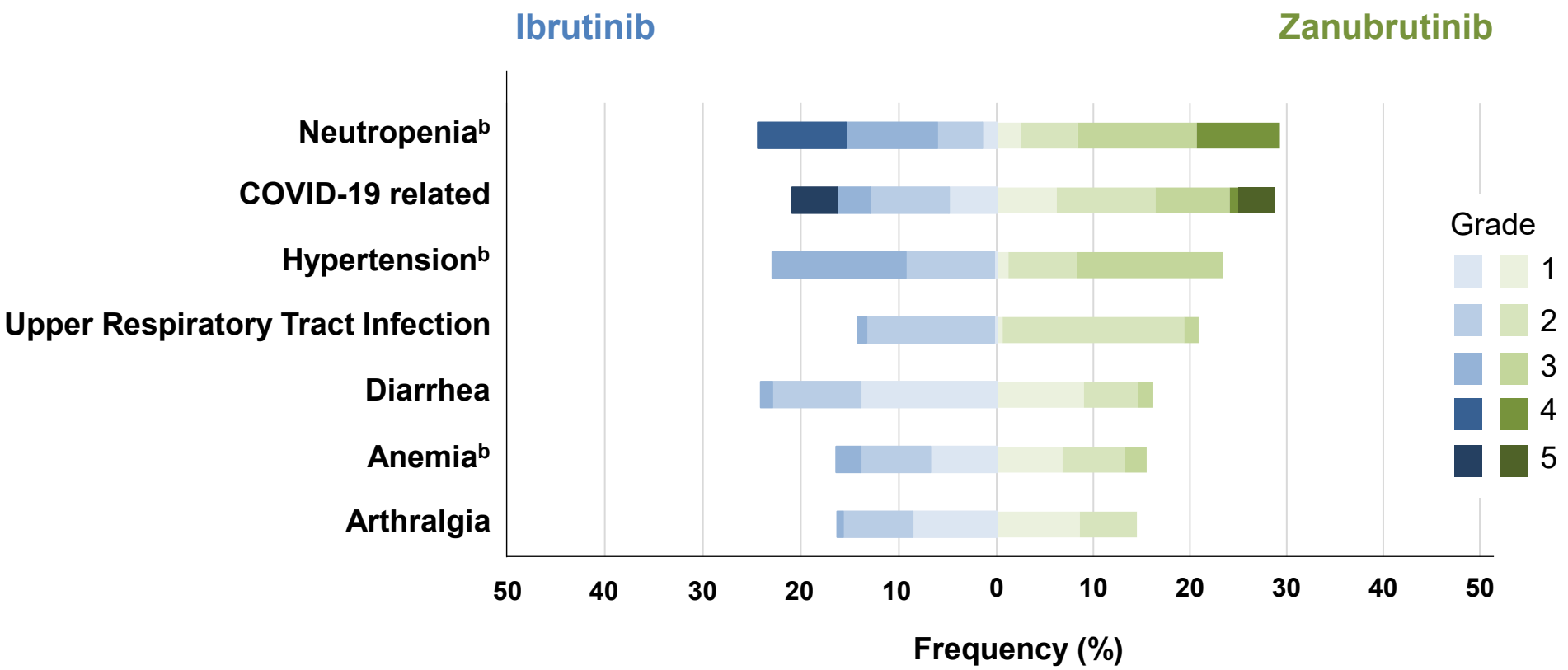
Most Common Adverse Events[a]



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

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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.

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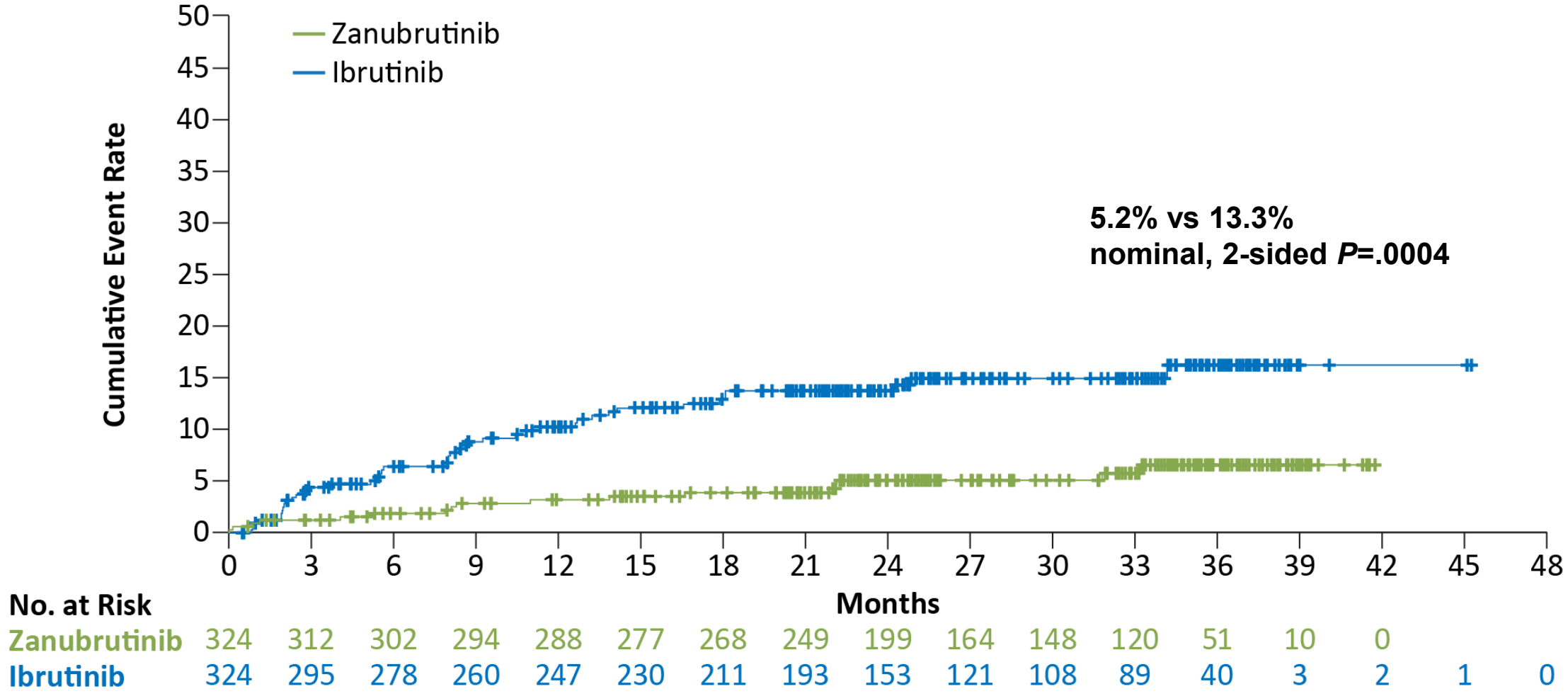
Fewer Atrial Fibrillation/Flutter Events With Zanubrutinib



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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 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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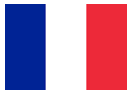

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Graf, Solomon
Chaudhry, Arvind

Coleman, Morton
Freeman, Benjamin
Bryan, Locke
Hall, Ryan
Twardy, Amanda
Hrom, John
Stevens, Don
Anz III, Bertrand
Bociek, Robert
Lamanna, Nicole

Sharman, Jeff
Burke, John
Santiago, Manuel
Ruxer, Robert
Farber, Charles

Zafar, Syed
Cultrera, Jennifer
Kambhampati, Suman
Eradat, Herbert

Robak T, et al. Zanubrutinib Demonstrated Superior Progression-Free Survival vs Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: Final Analysis of Phase 3 ALPINE Study.
Presented at: 31st Congress of the Polish Society of Hematology and Transfusion Medicine; September 14-16, 2023; Katowice, Poland. Correspondence: Tadeusz Robak; robaktad@csk.umed.lodz.pl

The NEW ENGLAND JOURNAL of MEDICINE

Original Article

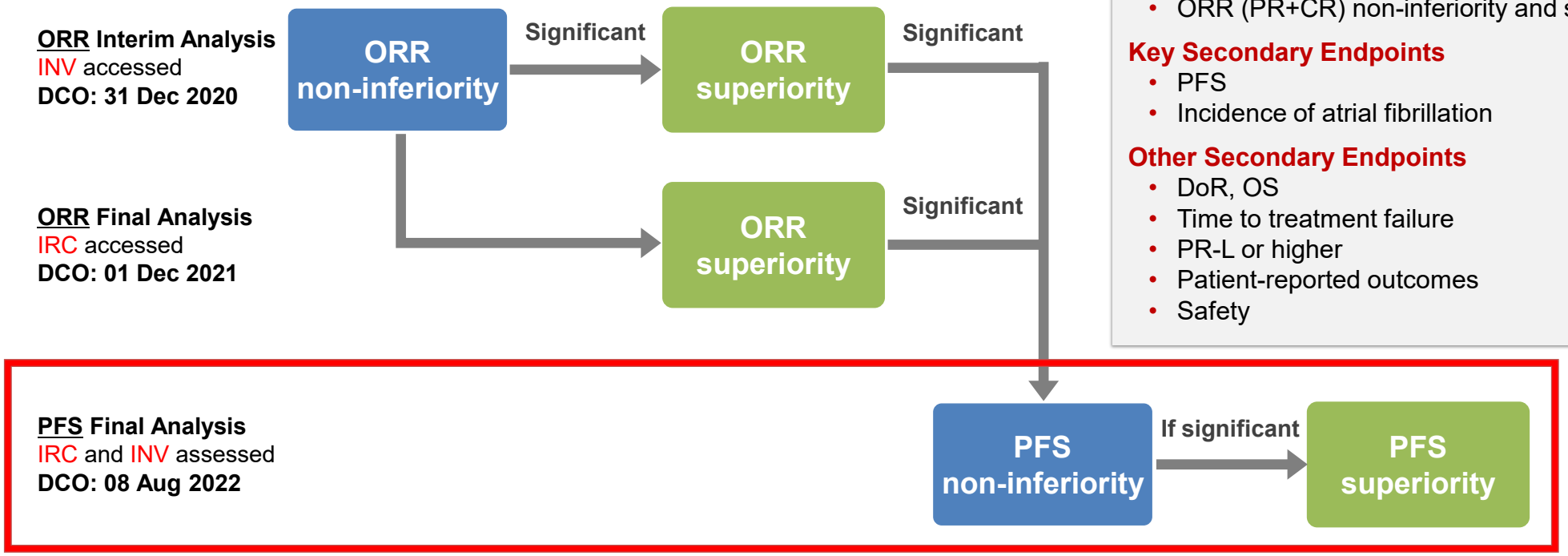
Zanubrutinib or Ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia

Robak T, et al. Zanubrutinib Demonstrated Superior Progression-Free Survival vs Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: Final Analysis of Phase 3 ALPINE Study. Presented at: 31st Congress of the Polish Society of Hematology and Transfusion Medicine; September 14-16, 2023; Katowice, Poland. Correspondence: Tadeusz Robak; robaktad@csk.umed.lodz.pl

Backup Slides

Endpoints and Statistical Design

- ORR non-inferiority and superiority were demonstrated in the ORR interim and final analyses; PFS was tested for non-inferiority under hierarchical testing when 205 events had occurred



Primary Endpoint
- ORR (PR+CR) non-inferiority and superiority (by INV)

Key Secondary Endpoints
- PFS
- Incidence of atrial fibrillation

Other Secondary Endpoints
- DoR, OS
- Time to treatment failure
- PR-L or higher
- Patient-reported outcomes
- Safety

CR, complete response; DCO, data cutoff; DoR, duration of response; INV, investigator; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PR-L, partial response with lymphocytosis.

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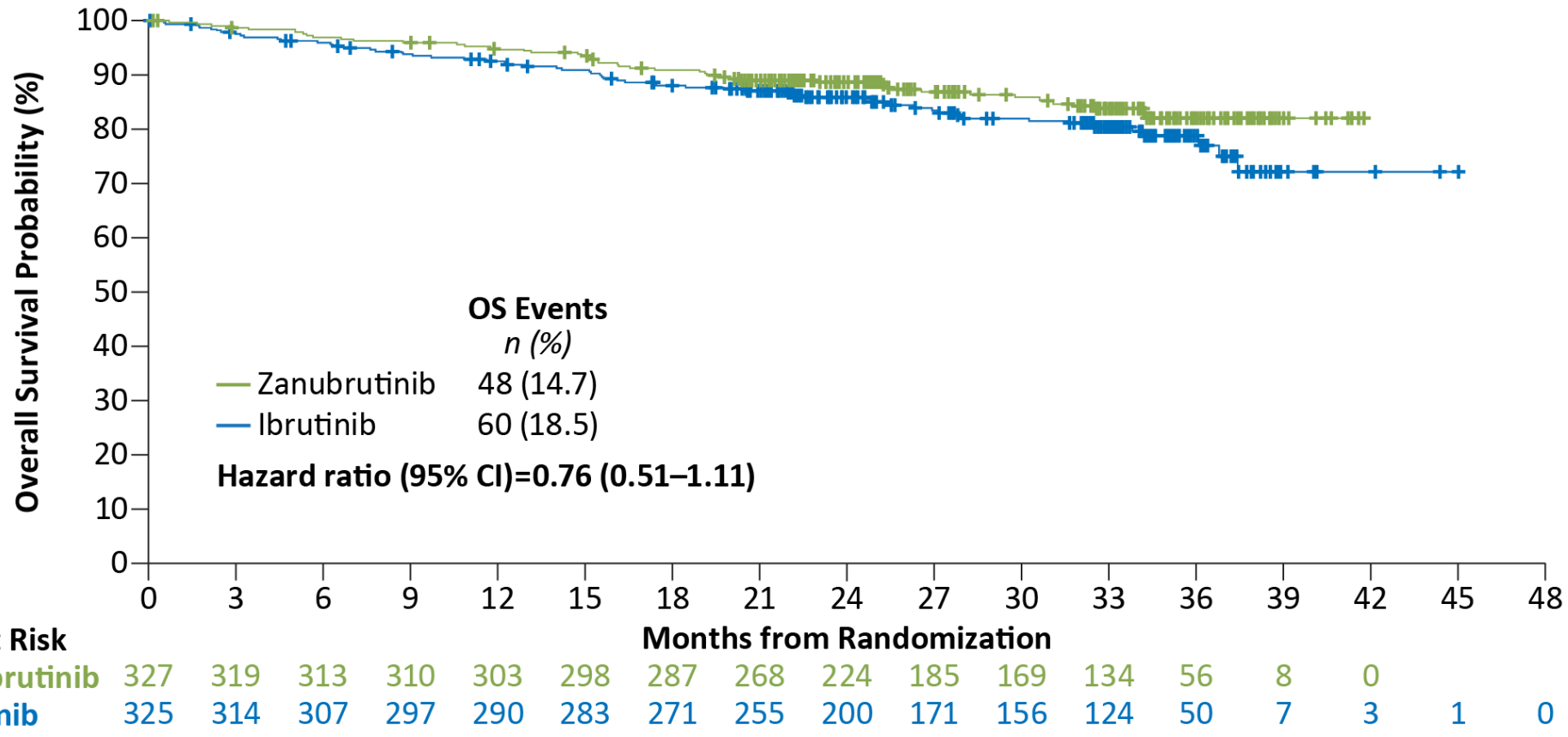
Overall Survival

- Fewer deaths with zanubrutinib compared with ibrutinib



CI, confidence interval; DCO, data cutoff; OS, overall survival.

DCO: 8 Aug 2022

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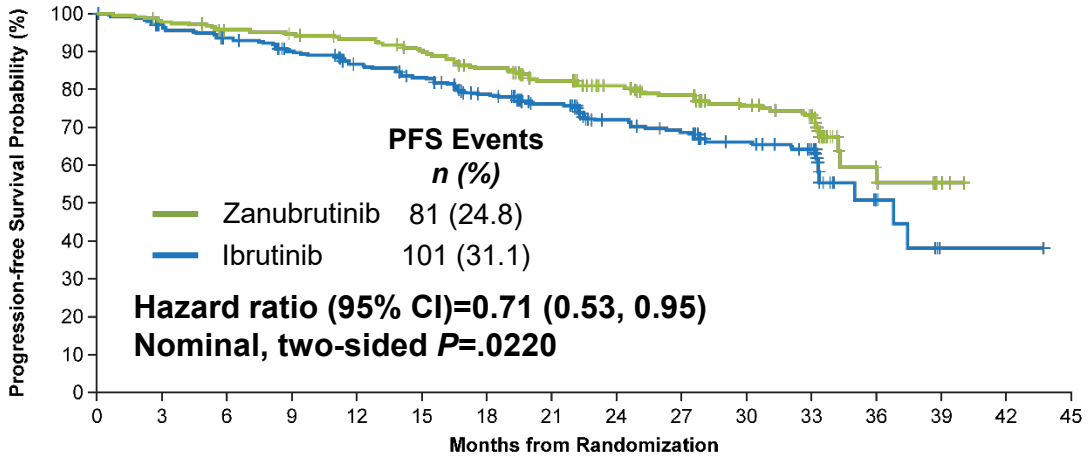
Sensitivity Analyses Are Consistent with Primary PFS Analysis, Including Drug Interruptions and Treatment Discontinuation

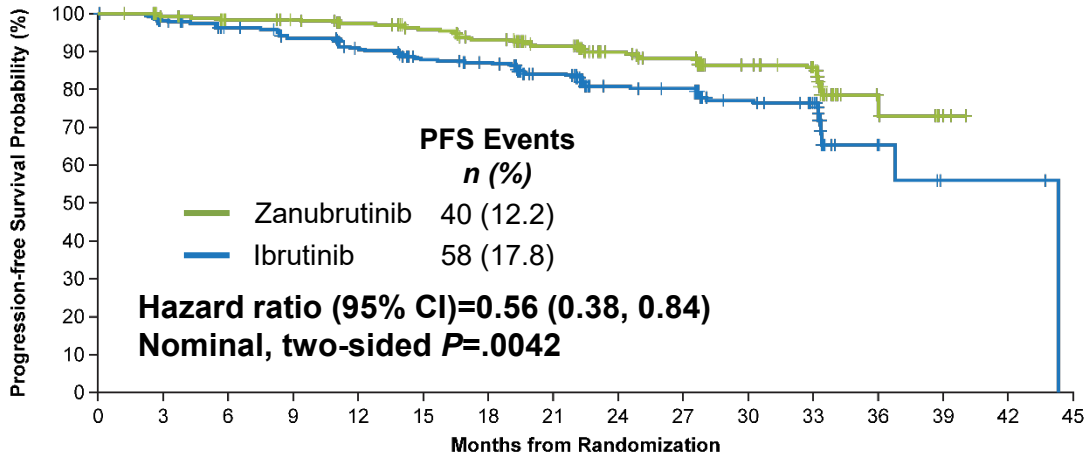
Drug Interruptions[1,2]



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

CI, confidence interval; DCO, data cutoff; PFS, progression-free survival.

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

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