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

Talha Munir[1], Jennifer R. Brown[2], Barbara Eichhorst[3], Peter Hillmen[4], Nicole Lamanna[5], Susan M. O'Brien[6], Constantine S. Tam[7,8], Lugui Qiu[9], Maciej Kaźmierczak[10], Wojciech Jurczak[11], Keshu Zhou[12], Martin Šimkovič[13,14], Jiří Mayer[15], Amanda Gillespie-Twardy[16], Alessandra Ferrajoli[17], Peter S. Ganly [18], Robert Weinkove[19,20], Sebastian Grosicki[21], Andrzej Mital[22], Tadeusz Robak[23], Anders Österborg[24,25], Habte A. Yimer[26], Tommi Salmi[27], Megan (Der Yu) Wang[27], Lina Fu[27], Jessica Li[27], Kenneth Wu[27], Aileen Cohen[27], and Mazyar Shadman[28,29]

[1]Leeds Hospital NHS Trust, Leeds, United Kingdom; [2]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [3]Department of Internal Medicine, University of Cologne, Center for Integrated Oncology Aachen, Bonn, Cologne, Duesseldorf, Cologne, Germany; [4]St James's University Hospital, Leeds, United Kingdom; [5]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY, USA; [6]Chao Family Comprehensive Cancer Center, University of California, Irvine, CA, USA; [7]The Alfred Hospital, Melbourne, Victoria, Australia; [8]Monash University, Melbourne, Victoria, Australia; [9]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Hematological Disorders, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China; [10]Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Poznan, Poland; [11]Maria Skłodowska-Curie National Research Institute of Oncology, Krakow, Poland; [12]Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China; [13]4th Department of Internal Medicine - Hematology, University Hospital, Hradec Kralove, Czech Republic; [14]Faculty of Medicine, Charles University, Prague, Czech Republic; [15]Department of Internal Medicine-Hematology and Oncology, Masaryk University and University Hospital, Brno, Czech Republic; [16]Blue Ridge Cancer Care, Roanoke, VA, USA; [17]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [18]Department of Haematology, Christchurch Hospital, Christchurch, New Zealand; [19]Te Rerenga Ora Blood and Cancer Centre, Te Whatu Ora Health New Zealand Capital Coast & Hutt Valley, Wellington, New Zealand; [20]Cancer Immunotherapy Programme, Malaghan Institute of Medical Research, Wellington, New Zealand; [21]Department of Hematology and Cancer Prevention, Health Sciences Faculty, Medical University of Silesia, Katowice, Poland; [22]Department of Hematology and Transplantology, Medical University of Gdańsk, Gdańsk, Poland; [23]Medical University of Lodz, Lodz, Poland; [24]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; [25]Department of Hematology, Karolinska University Hospital, Stockholm, Sweden; [26]Texas Oncology-Tyler/US Oncology Research, Tyler, TX, USA; [27]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; [28]Fred Hutchinson Cancer Center, Seattle, WA, USA; and [29]Department of Medicine, University of Washington, Seattle, WA, USA

Disclosures for Dr. Munir

Honoraria from Janssen, AstraZeneca, Alexion, Sobi, Novartis, Roche, Abbvie, Gilead; member of the board of directors or advisory committee for Janssen, AstraZeneca, Alexion, Abbvie, Novartis, Roche.

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[3-6]
  - Exposure coverage between dosing intervals falls below IC_{50} and variable BTK occupancy at trough has been observed

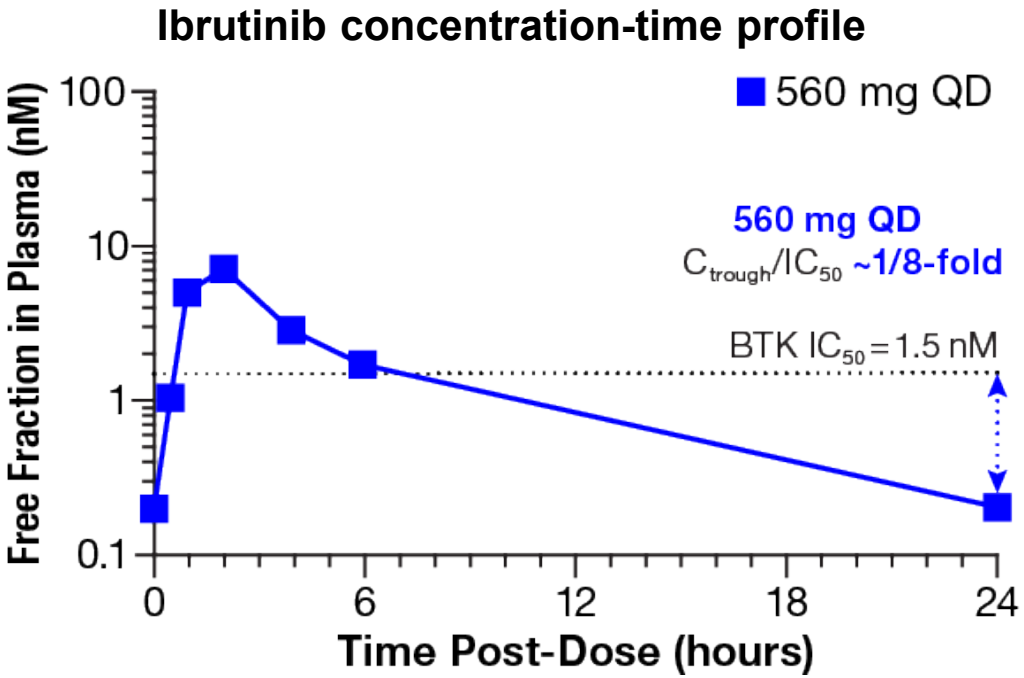


Figure adapted from Tam CS et al. *Expert Rev Clin Pharmacol*. 2021;14:11, 1329-1344.

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. Molis S, et al. *Hematol Oncol*. 2020; 38: 129-136. 3. Sharman JP, et al. *Blood*. 2017;130(suppl 1):4060. 4. Mato AR, et al. *Haematologica*. 2018;103(5):874-879.
5. Munir T, et al. *Am J Hematol*. 2019;94(12):1353-1363. 6. Ghia P, et al. EHA Abstract EP636 2021.

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 in treatment-naive CLL/SLL patients without del(17p)[1]

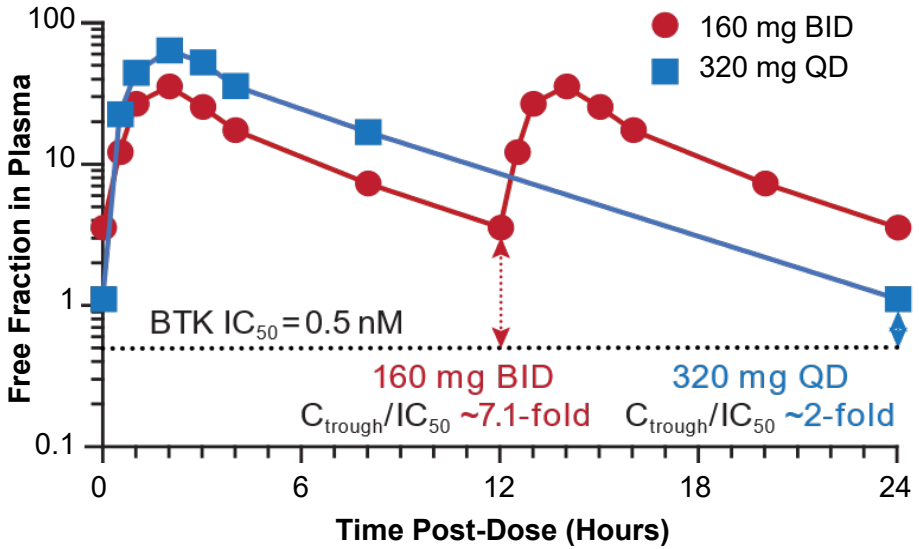


Figure modified from Ou YC, et al *Leukemia & Lymphoma*. 2021; 62(11):2612-2624.

BID, twice daily; BTK, Bruton tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; del(17p), deletion in chromosome 17p; IC_{50}, 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.

ALPINE Study Design

R/R CLL/SLL with ≥ 1 prior treatment

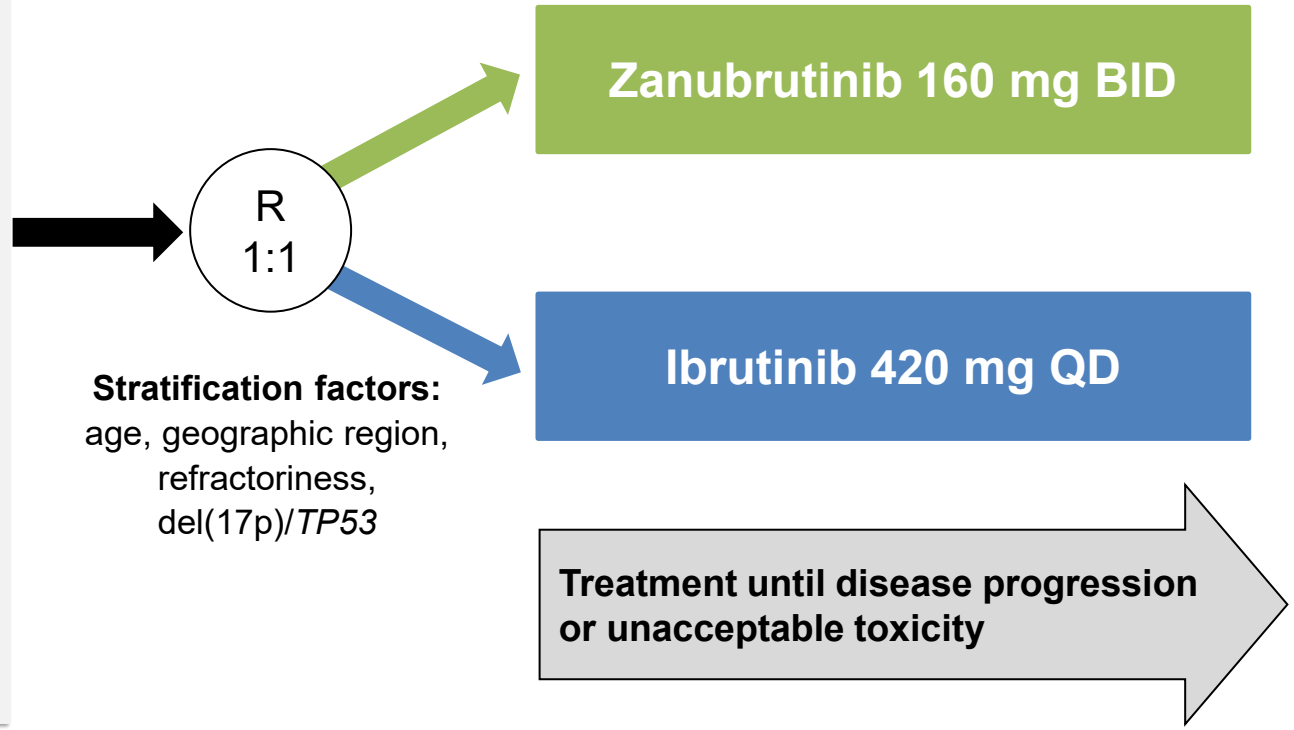
(Planned N=600, Actual N=652)

Key Inclusion Criteria

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

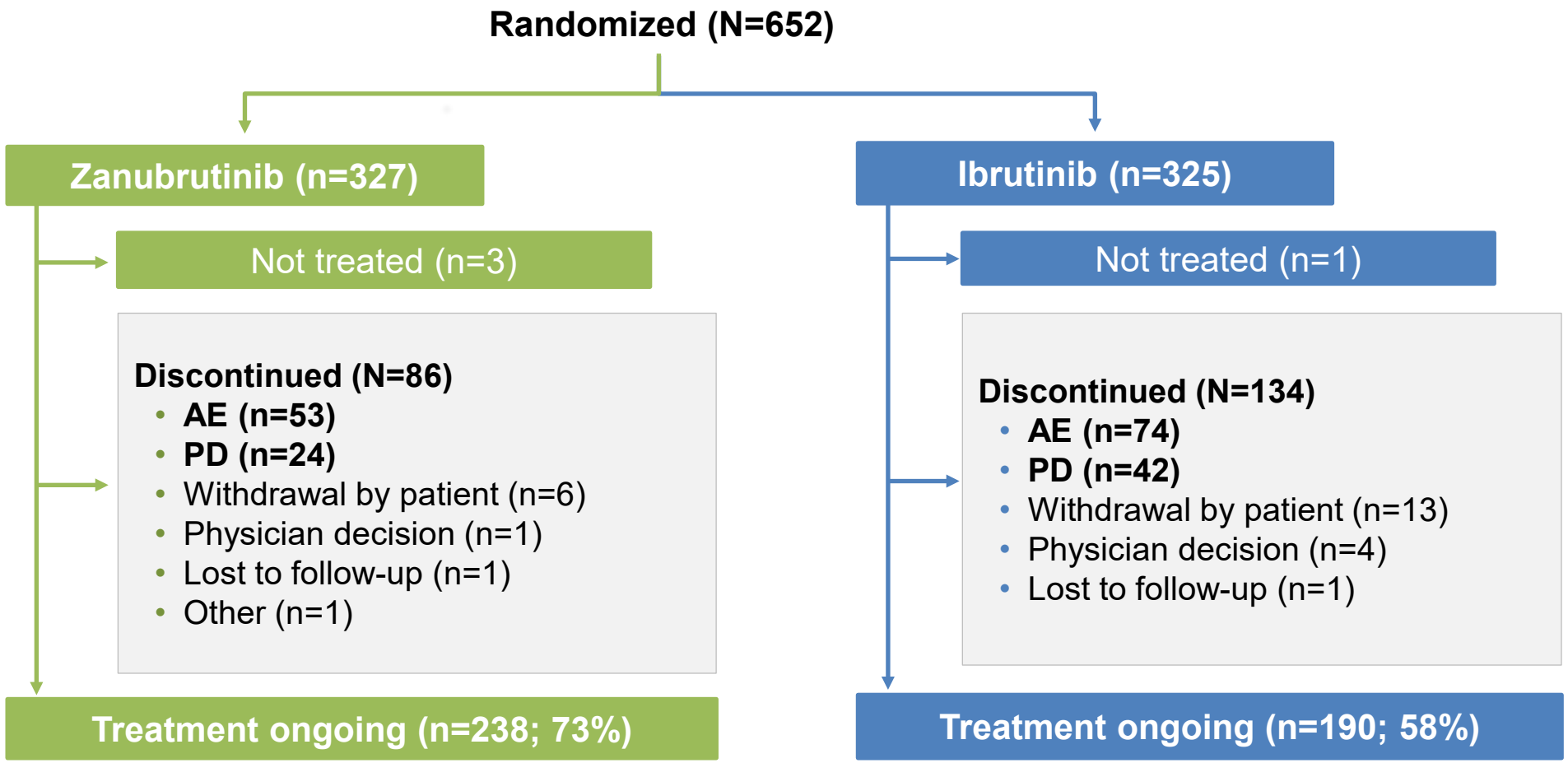
Key Exclusion Criteria

- 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.

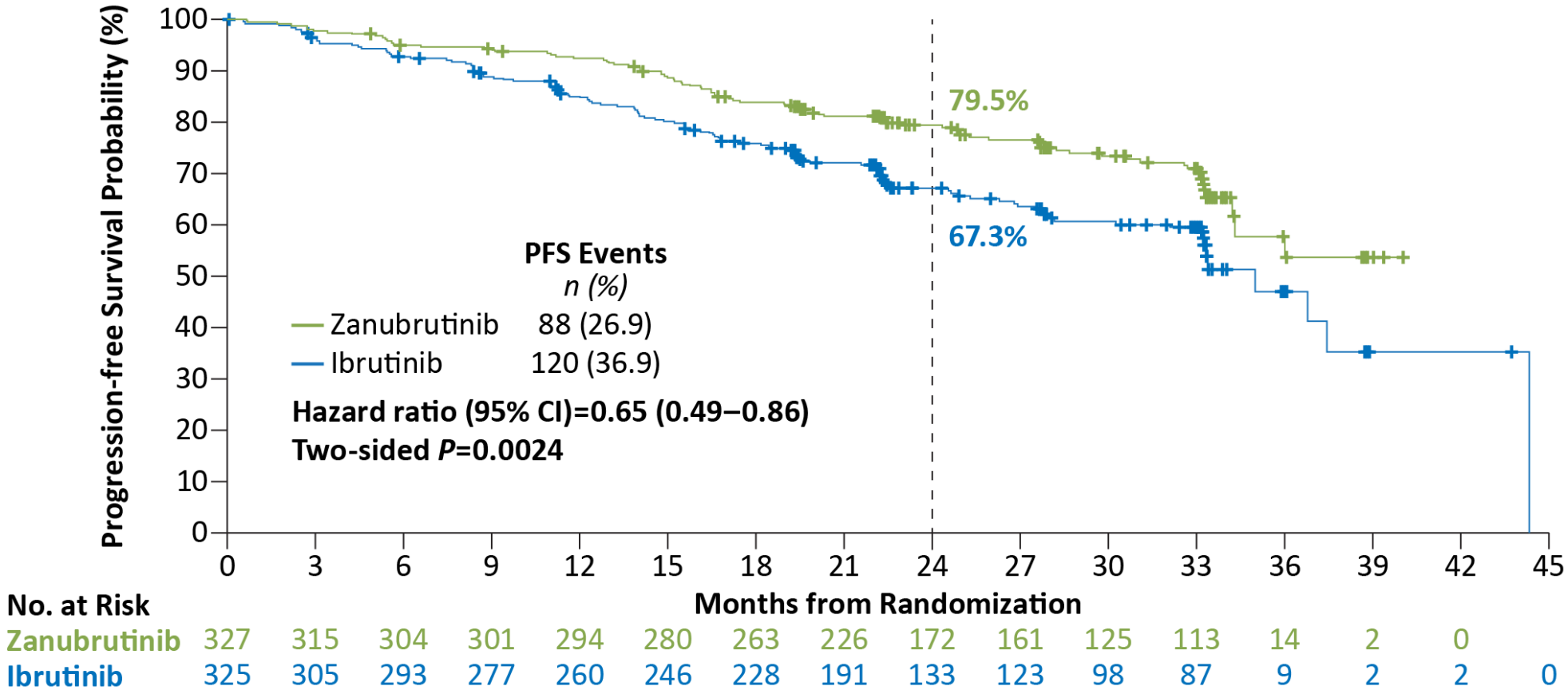
Balanced Demographics and Disease Characteristics

	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

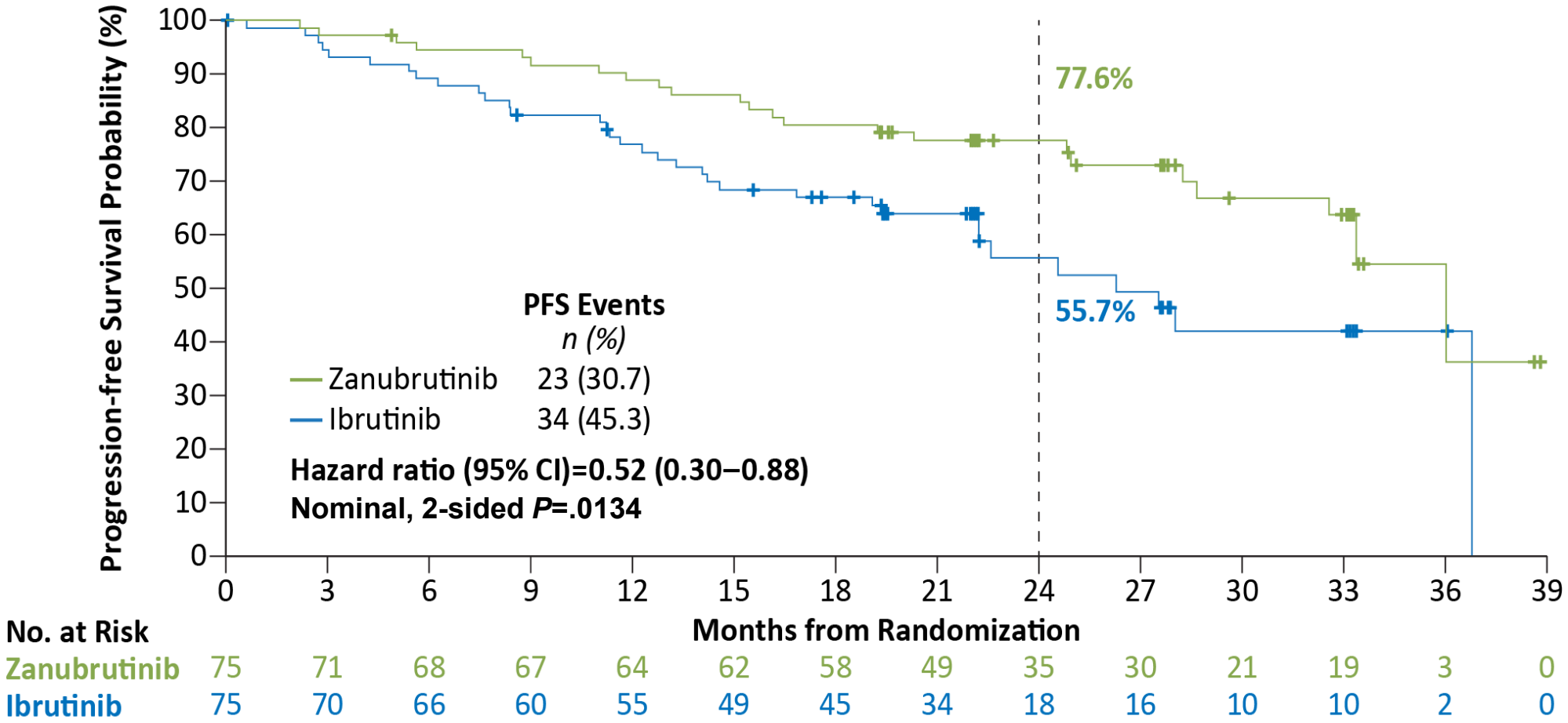
- Median study follow-up of 29.6 months



DCO: 8 Aug 2022

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

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

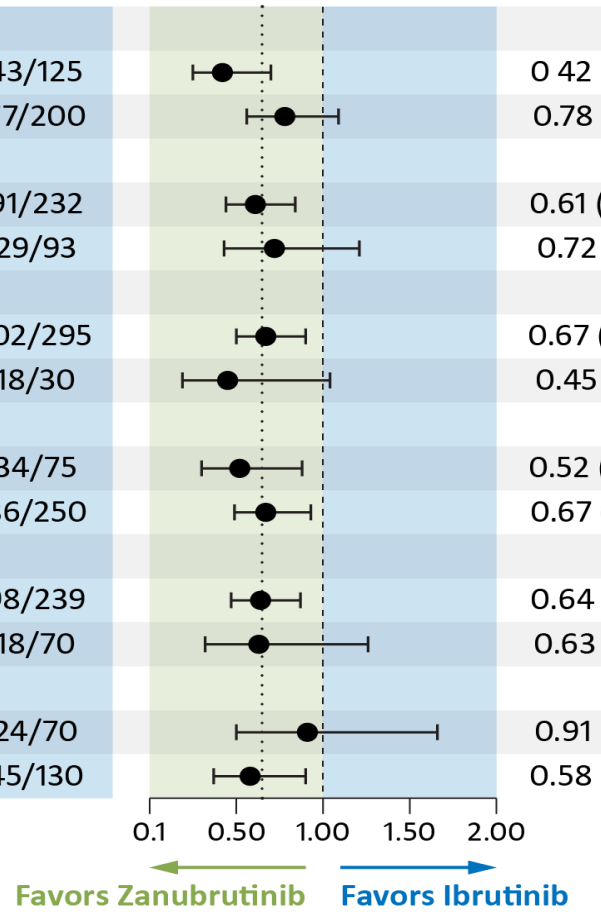


DCO: 8 Aug 2022

[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.

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)

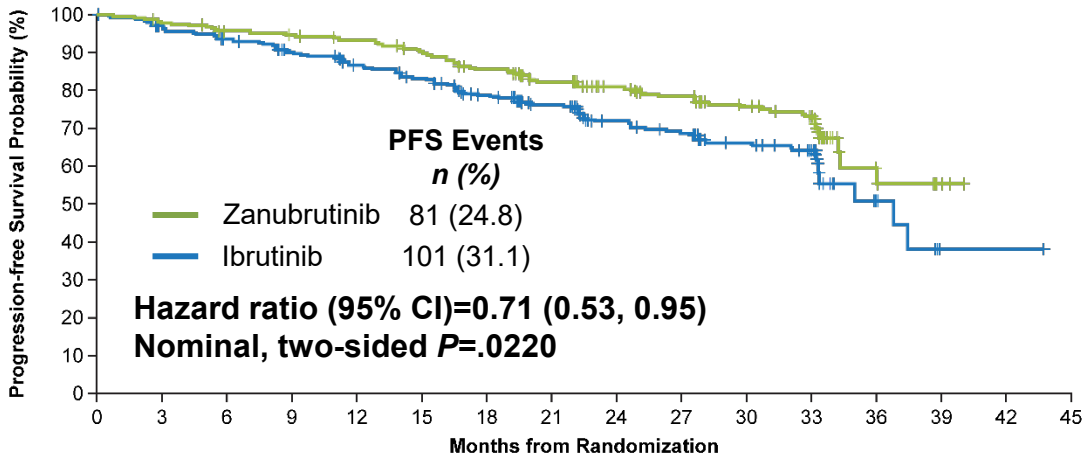


DCO: 8 Aug 2022

[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.

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

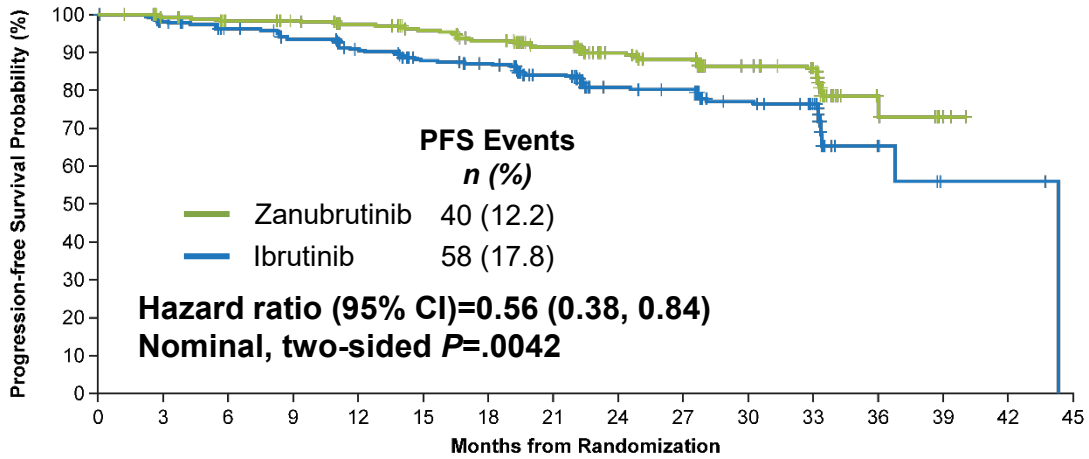
Drug Interruptions[1,2]



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]

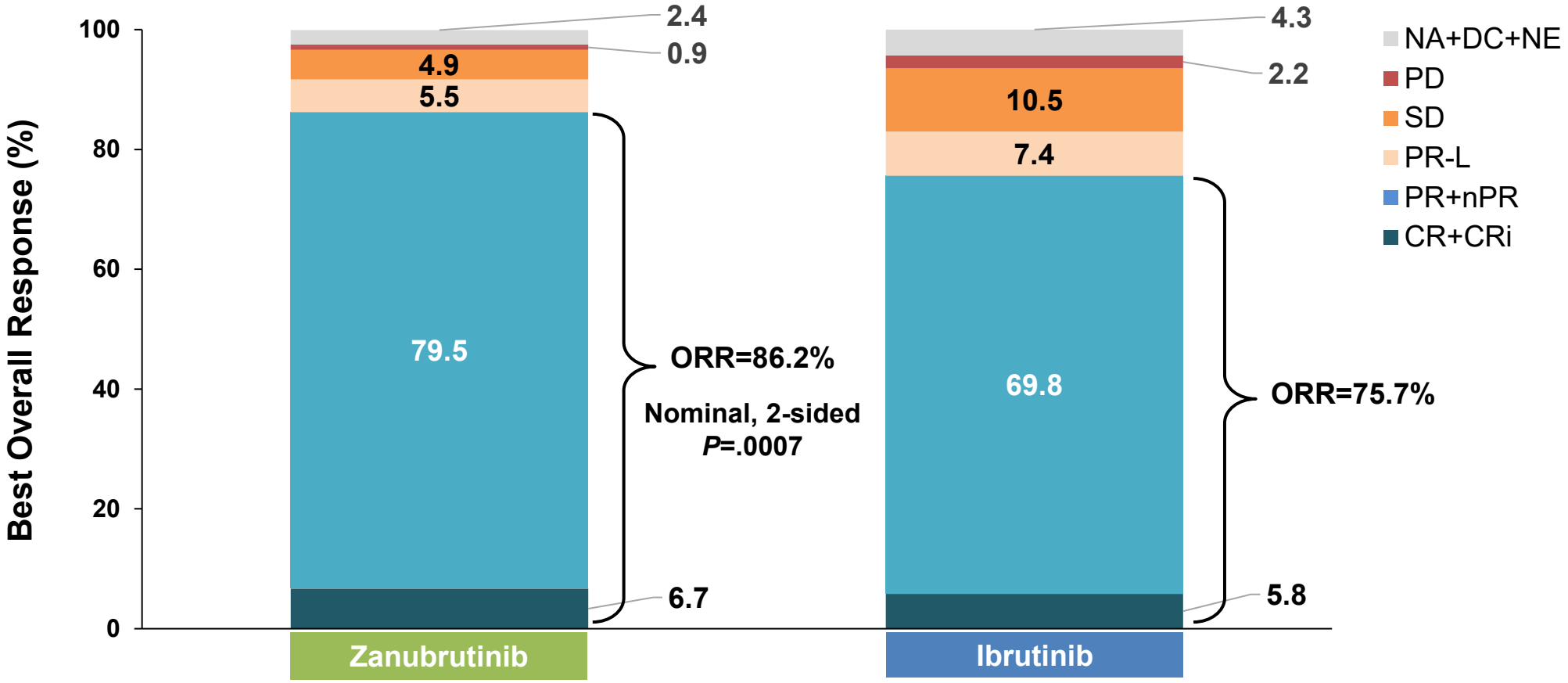


No. of Patients at Risk

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.
CI, confidence interval; 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.

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; 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

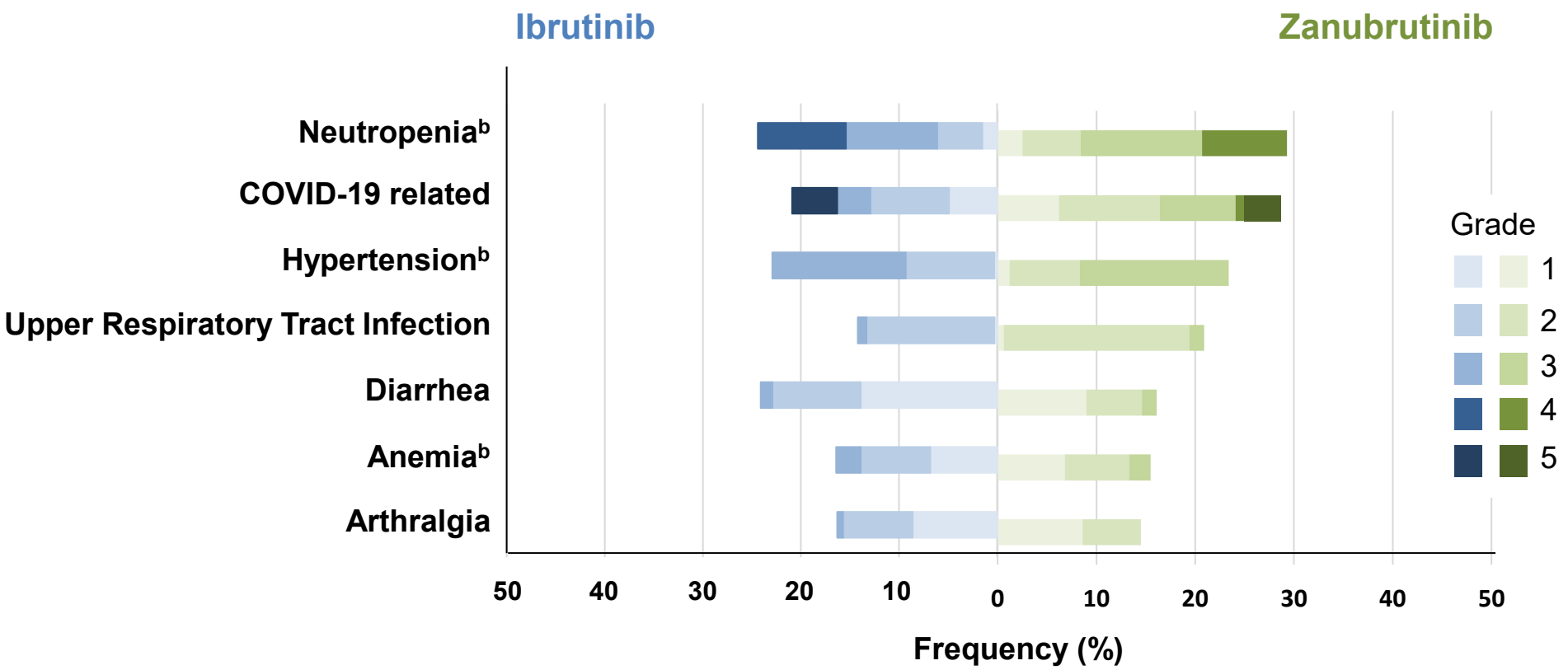
- Zanubrutinib safety profile was more favorable compared with ibrutinib

	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)**

DCO: 8 Aug 2022

AE, adverse event; DCO, data cutoff.

Most Common AEs[a]



DCO: 8 Aug 2022

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

Zanubrutinib had a Favorable Cardiac Profile

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

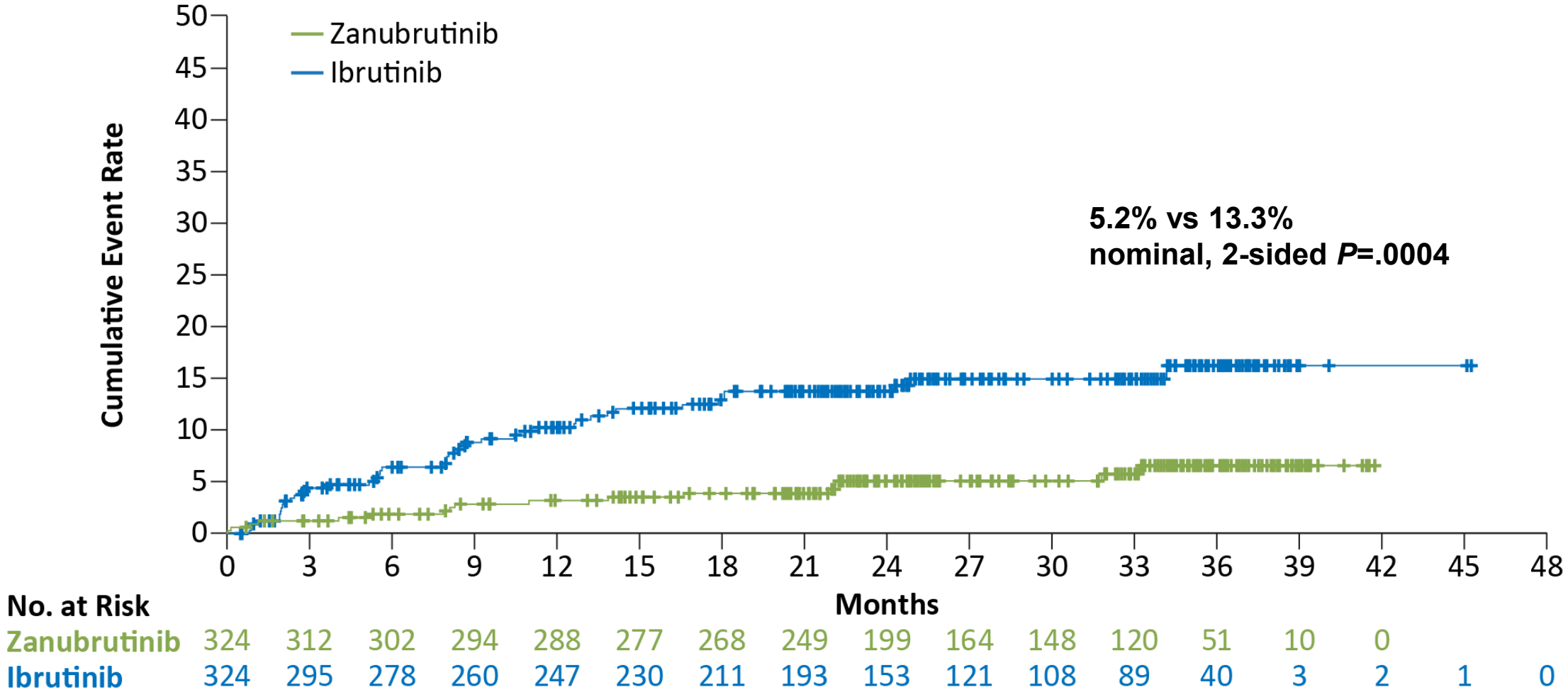
- Lower rate of serious cardiac AEs reported with zanubrutinib
  - Atrial fibrillation/flutter (n=2)
  - MI/ACS (n=2)
  - CHF (n=2)
- **Fatal cardiac events:**
  - **Zanubrutinib, n=0 (0%)**
  - **Ibrutinib, n=6 (1.9%)**

	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)

DCO: 8 Aug 2022

[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; MI, myocardial infarction.

Fewer Atrial Fibrillation/Flutter Events With Zanubrutinib



DCO: 8 Aug 2022

DCO, data cutoff.

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**

Acknowledgments

- We would like to thank our independent data monitoring committee members for their efforts in this study.
- Additionally, we would like to thank the BeiGene ALPINE study team for all their efforts and hard work.
- Assistance with medical writing and editorial support, under the direction of the authors, was provided by ArticulateScience, LLC, and was funded by BeiGene in accordance with Good Publication Practice (GPP) guidelines (http://www.ismpp.org/gpp-2022).

Correspondence:

Talha Munir; email: tmunir@nhs.net