Extended Follow-up of the Phase 3 ALPINE Study of Zanubrutinib Versus Ibrutinib in R/R CLL/SLL

Talha Munir, MD, PhD[1]; Barbara Eichhorst, MD[2]; Peter Hillmen, MD, PhD[3]; Nicole Lamanna, MD[4]; Susan M. O'Brien, MD[5]; Constantine S. Tam, MBBS, MD[6]; Lugui Qiu, MD[7]; Tommi Salmi, MD[8]; Kenneth Wu, PhD[9]; Jennifer R. Brown, MD, PhD[10]

[1]Leeds Teaching Hospital NHS Trust, Leeds, United Kingdom; [2]University of Cologne, Center for Integrated Oncology Aachen, Germany; [3]St James's University Hospital, Leeds, United Kingdom; [4]Herbert Irving Comprehensive Cancer Center, Columbia University, New York NY, USA; [5]Chao Family Comprehensive Cancer Center, University of California, Irvine CA, USA; [6]The Alfred Hospital, Melbourne Victoria, Australia; [7]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; [8]BeiGene International GmbH, Basel, Switzerland; [9]BeiGene USA, Inc, San Mateo CA, USA; [10]Dana-Farber Cancer Institute, Boston MA, USA

Disclosures

TM: Honoraria: Janssen, AbbVie, Gilead, Alexion, Novartis, Roche; Consulting role: MorphoSys, Sunesis. **BFE**: Research funding: Janssen, Gilead, Roche, AbbVie, BeiGene, AstraZeneca; Honoraria: Janssen, BeiGene, Roche, AbbVie, Novartis, Celgene, AstraZeneca; Speakers bureau: Roche, AbbVie, MSD, BeiGene, AstraZeneca; Travel, accommodations, expenses: BeiGene. **PH:** Grant support: Janssen, Abbvie. **NL**: Consultancy: AbbVie, AstraZeneca, BeiGene, Lilly/Loxo, Genentech, Janssen, Pharmacyclics; Research funding: AbbVie, AstraZeneca, BeiGene, Lilly/Loxo, Genentech, Octapharma, Oncternal, MingSight, TG Therapeutics. **SMO**: Consultancy: AbbVie, AstraZeneca, BeiGene, Lilly, Janssen, Johnson & Johnson, Pfizer, Pharmacyclics; Research Funding: BeiGene, Lilly, Pfizer, Pharmacyclics, Regeneron; Membership: CLL Society (unpaid). **CST**: Research funding: Janssen, AbbVie, BeiGene; Honoraria: Janssen, AbbVie, BeiGene, Loxo, AstraZeneca. **LQ**: Consultancy and Speakers bureau: Janssen, AstraZeneca, Takeda, Roche, AbbVie, BeiGene. **TS, KW**: Employment: BeiGene; Equity Holder: BeiGene. **JRB**: Consultancy: Abbvie, Acerta/AstraZeneca, Alloplex Biotherapeutics, BeiGene, Galapagos NV, Genentech/Roche, Grifols Worldwide Operations, InnoCare Pharma Inc, iOnctura, Kite, Loxo/Lilly, Merck, Numab Therapeutics, Pfizer, Pharmacyclics; Research funding from BeiGene, Gilead, iOnctura, Loxo/Lilly, MEI Pharma, TG Therapeutics.

Zanubrutinib Is a Differentiated BTKi With High Potency, Bioavailability, and Selectivity

- Zanubrutinib is highly selective for BTK and has potent inhibitory activity against BTK[1]
- Zanubrutinib has no active metabolite; ibrutinib and acalabrutinib each have an active metabolite (PCI-45227 and M27, respectively) with activity on kinases other than BTK[1]
- Zanubrutinib has continuous exposure coverage above its IC_{50} compared with ibrutinib[2] and acalabrutinib[3]
  - Higher drug-concentration/IC_{50} ratios would be expected to lead to more sustained and complete BTK inhibition to improve efficacy

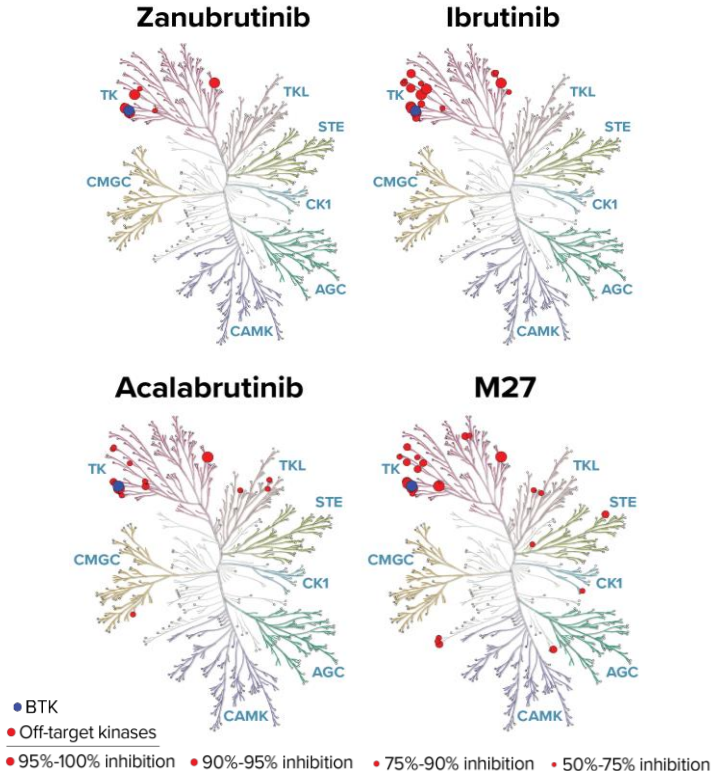


Figure adapted from Shadman et al. *Lancet Haematol.* 2023.

[1]Tam et al. *Blood Cancer J.* 2023; [2]Ou, et al. *Leuk Lymphoma*. 2021; [3]Marostica et al. *Cancer Chemother Pharmacol*. 2015.
BTK, Bruton tyrosine kinase; IC_{50}, half-maximal concentration.

ALPINE Study Design (NCT03734016)

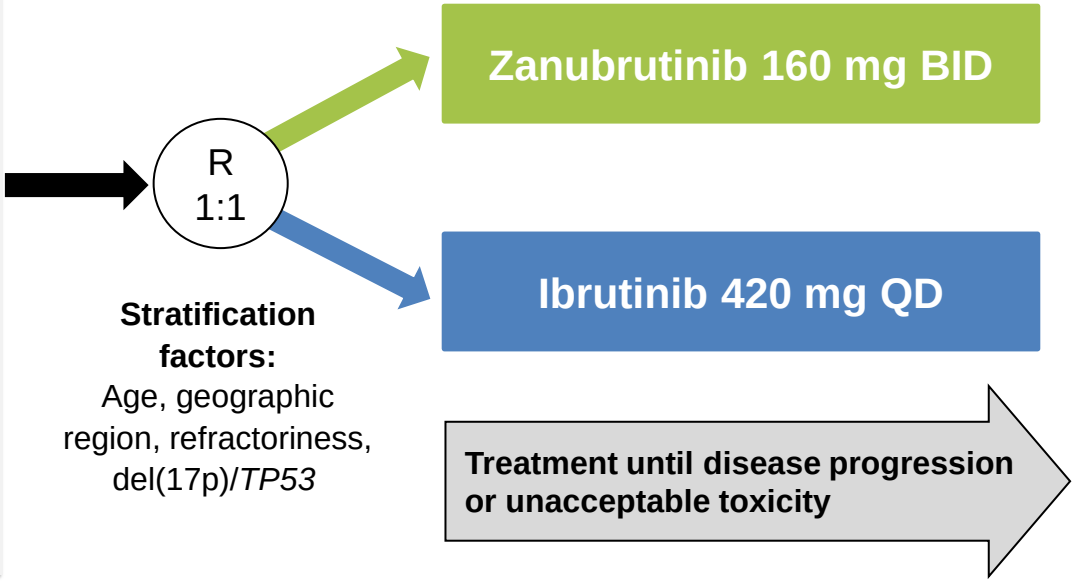
R/R CLL/SLL with ≥1 prior treatment
(N=652)

Key Inclusion Criteria

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

Key Exclusion Criteria

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



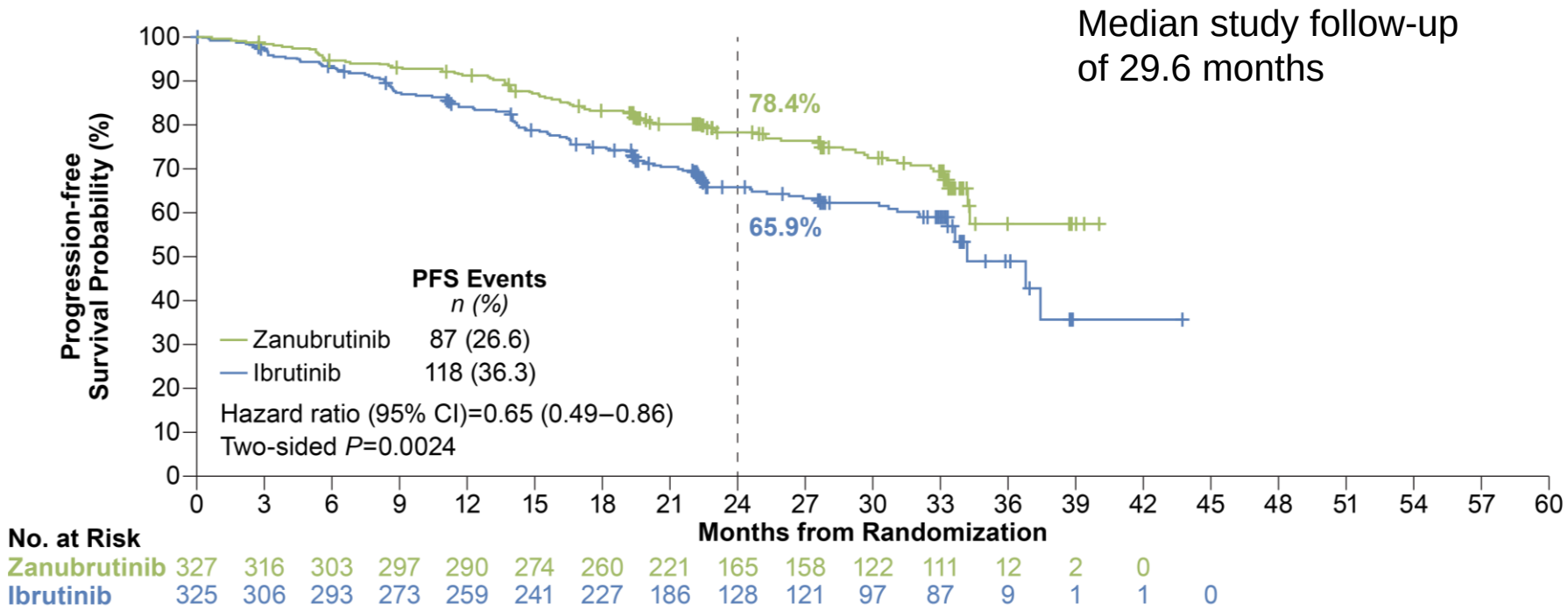
Brown JR, Eichhorst B, Hillmen P, et al. *N Engl J Med*. 2023;388:319-332.
BID, twice daily; CLL/SLL, chronic lymphocytic leukemia or small lymphocytic lymphoma; CT, computed tomography; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRI, magnetic resonance imaging; QD, once daily; R, randomized; R/R, relapsed or refractory.

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)
IGHV mutational status, n (%) Mutated Unmutated	 80 (24.5) 240 (73.4)	 70 (21.5) 241 (74.2)
Complex karyotype[a]	**56 (17.1)**	**70 (21.5)**
Bulky disease (≥5 cm), n (%)	**145 (44.3)**	**149 (45.8)**

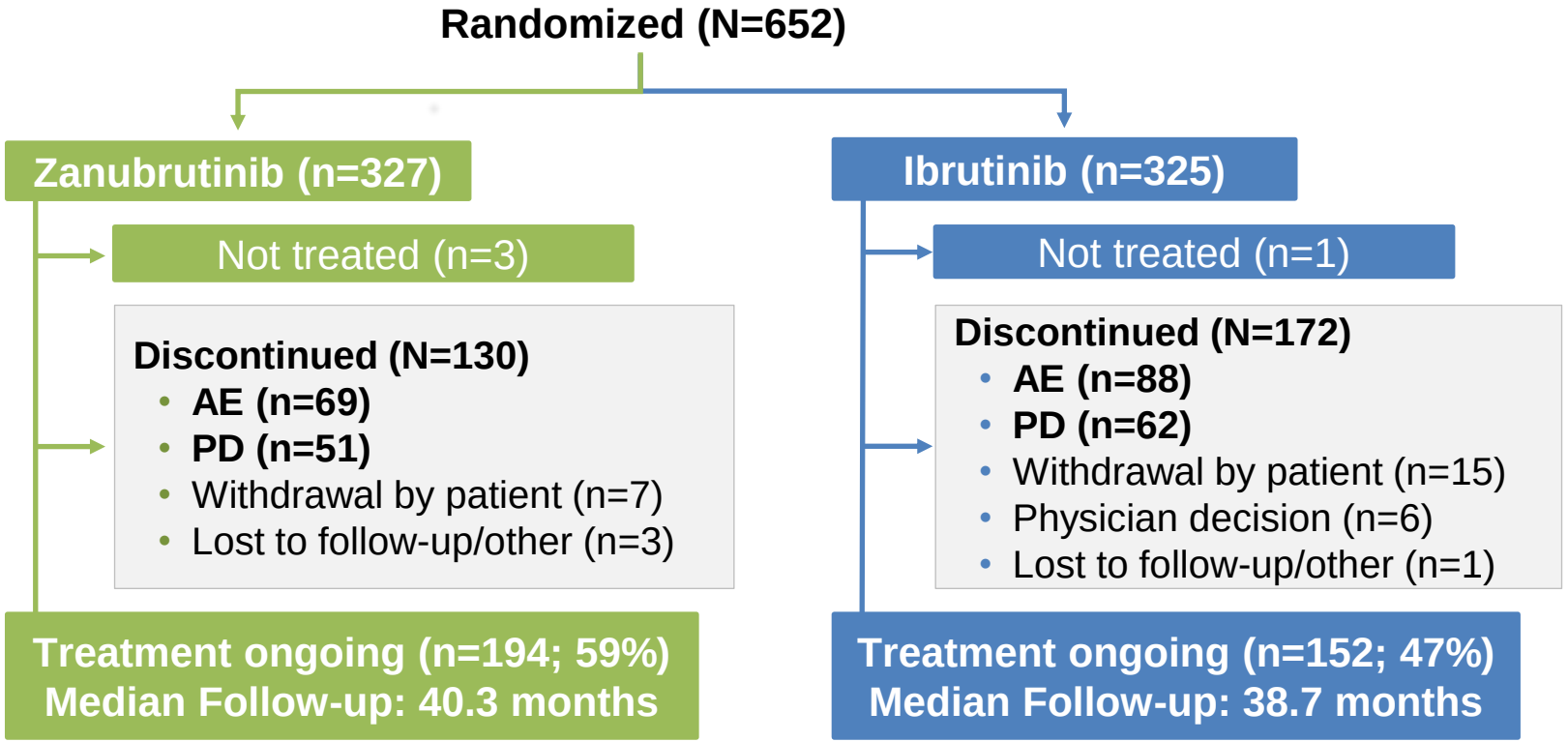
Data cutoff: 15 Sep 2023.
[a] Complex karyotype is defined as having ≥3 abnormalities.
Brown JR, Eichhorst B, Hillmen P, et al. *N Engl J Med*. 2023;388:319-332.
ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin variable heavy chain.

Previous Report Demonstrated Zanubrutinib is Clinically and Statistically Superior to Ibrutinib



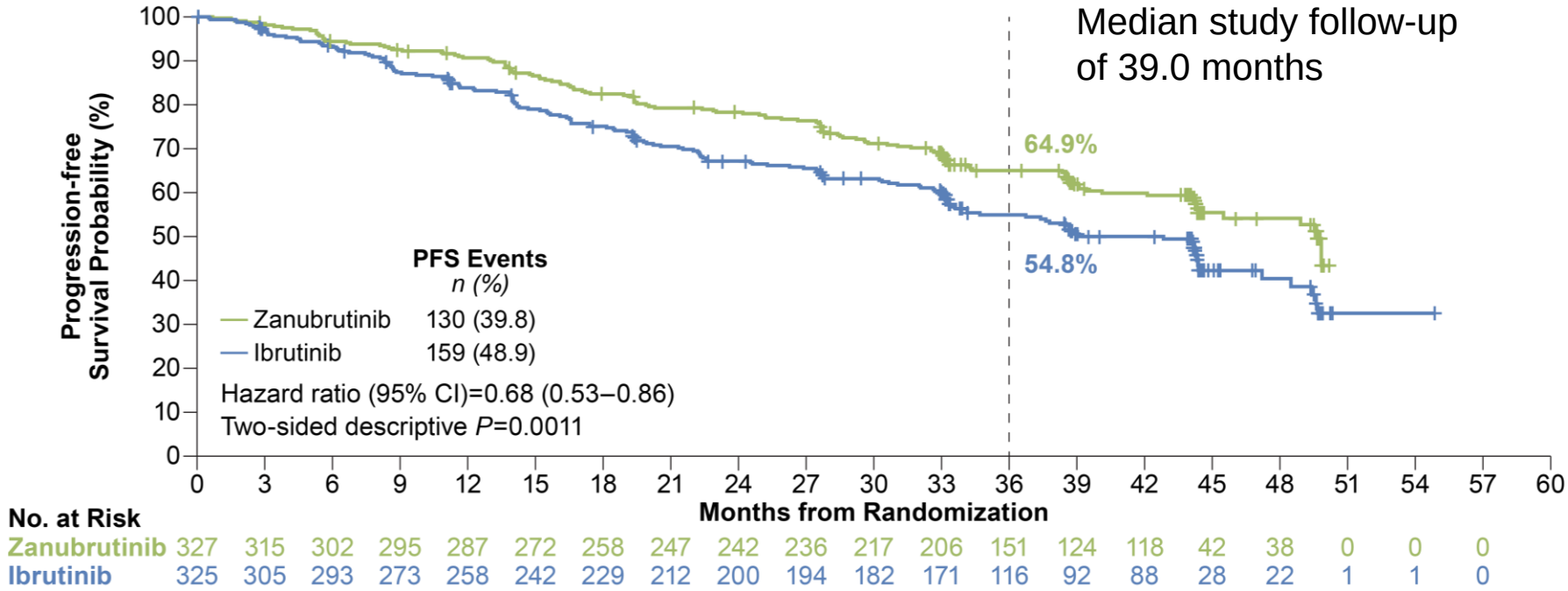
Data cutoff: 8 Aug 2022.
Brown JR, Eichhorst B, Hillmen P, et al. *N Engl J Med*. 2023;388:319-332.
PFS, progression-free survival.

Patient Disposition at Extended Follow-up



Data cutoff: 15 Sep 2023.
AE, adverse event; PD, progressive disease.

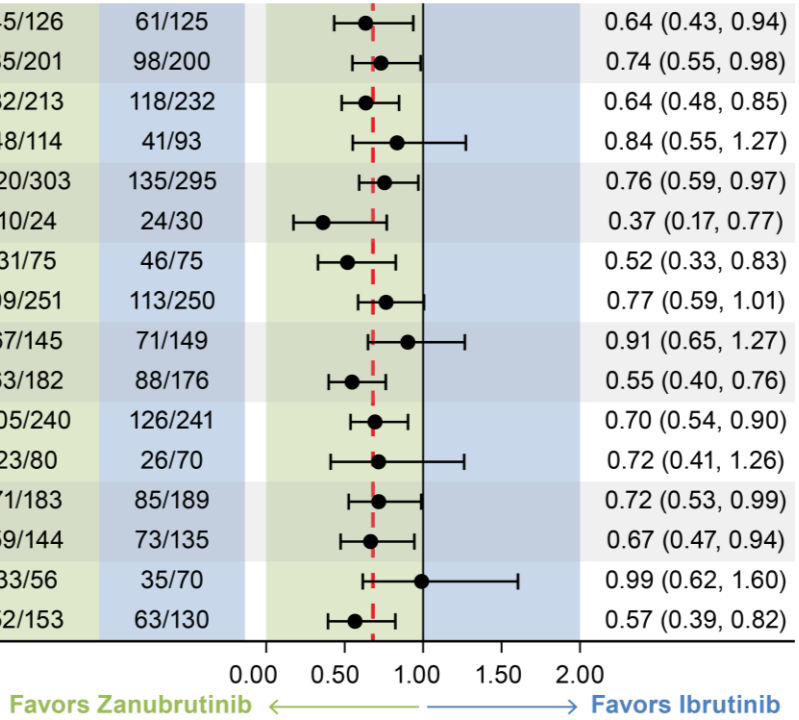
Zanubrutinib Sustains PFS Benefit Over Ibrutinib at Extended Follow-up



Data cutoff: 15 Sep 2023.
PFS, progression-free survival.

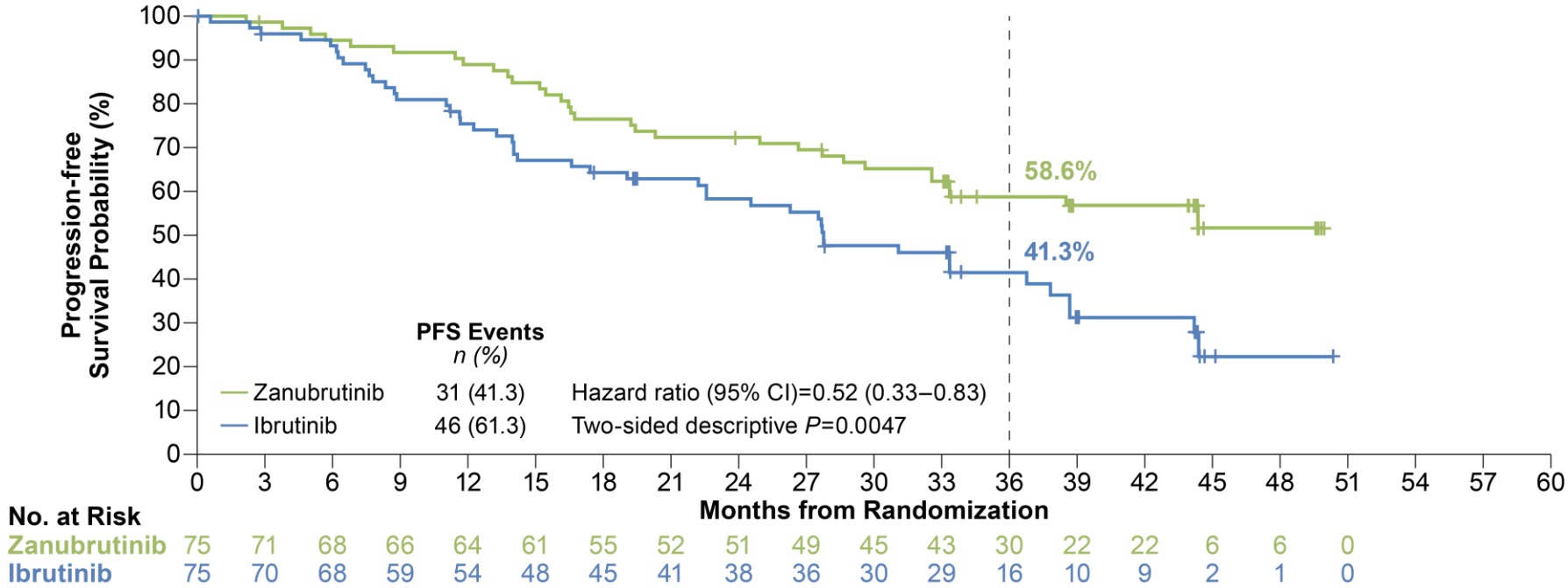
PFS Favored Zanubrutinib Across Subgroups

Subgroup		Zanubrutinib Events/Patients	Ibrutinib Events/Patients	Hazard Ratio (95% CI)
Age group	<65 years	45/126	61/125	0.64 (0.43, 0.94)
	≥65 years	85/201	98/200	0.74 (0.55, 0.98)
Sex	Male	82/213	118/232	0.64 (0.48, 0.85)
	Female	48/114	41/93	0.84 (0.55, 1.27)
Prior lines of therapy	1-3	120/303	135/295	0.76 (0.59, 0.97)
	>3	10/24	24/30	0.37 (0.17, 0.77)
Baseline del(17p)/ *TP53* mutation status	Present	31/75	46/75	0.52 (0.33, 0.83)
	Absent	99/251	113/250	0.77 (0.59, 1.01)
Bulky disease	Yes	67/145	71/149	0.91 (0.65, 1.27)
	No	63/182	88/176	0.55 (0.40, 0.76)
Baseline IGHV mutation status	Unmutated	105/240	126/241	0.70 (0.54, 0.90)
	Mutated	23/80	26/70	0.72 (0.41, 1.26)
Disease stage	Binet stage of A/B or Ann Arbor stage I/II bulky	71/183	85/189	0.72 (0.53, 0.99)
	Binet stage C or Ann Arbor stage III/IV	59/144	73/135	0.67 (0.47, 0.94)
Complex karyotype	Yes	33/56	35/70	0.99 (0.62, 1.60)
	No	52/153	63/130	0.57 (0.39, 0.82)



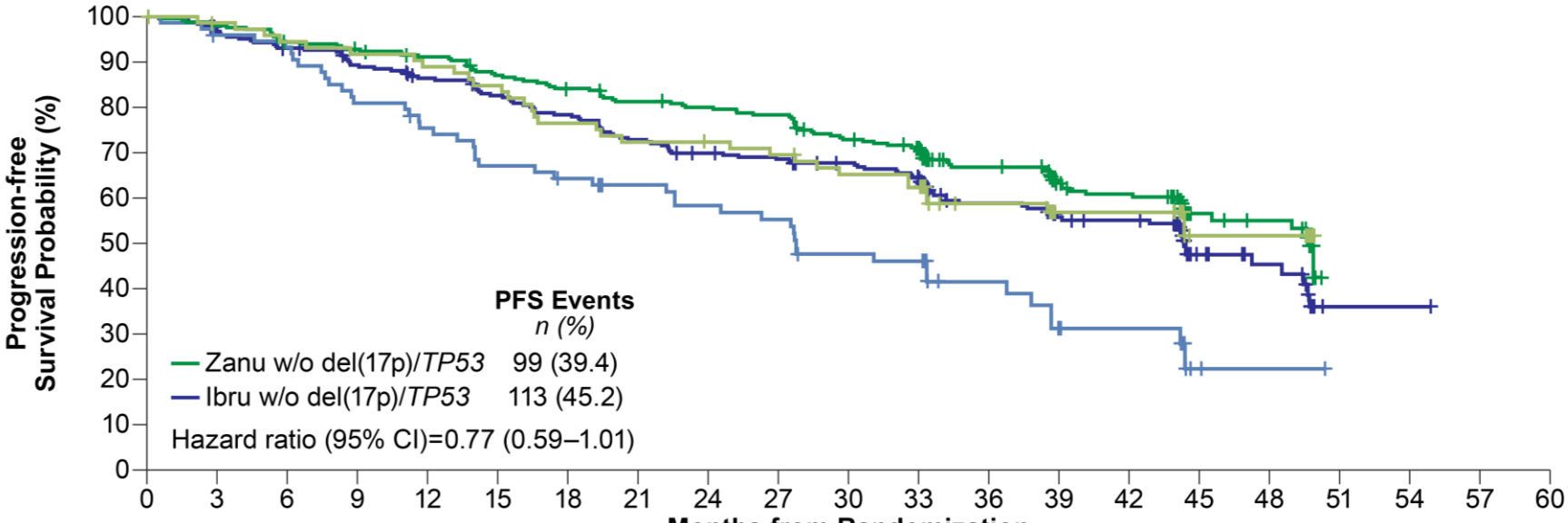
Data cutoff: 15 Sep 2023.
IGHV, immunoglobulin variable heavy chain; ITT, intention to treat; PFS, progression-free survival.

Improved PFS was Demonstrated With Zanubrutinib in Patients With del(17p)/*TP53*^{mut}



Data cutoff: 15 Sep 2023.
PFS, progression-free survival.

Zanubrutinib Demonstrated Robust PFS Benefit Independent of del(17p)/*TP53*^{mut} Mutation Status

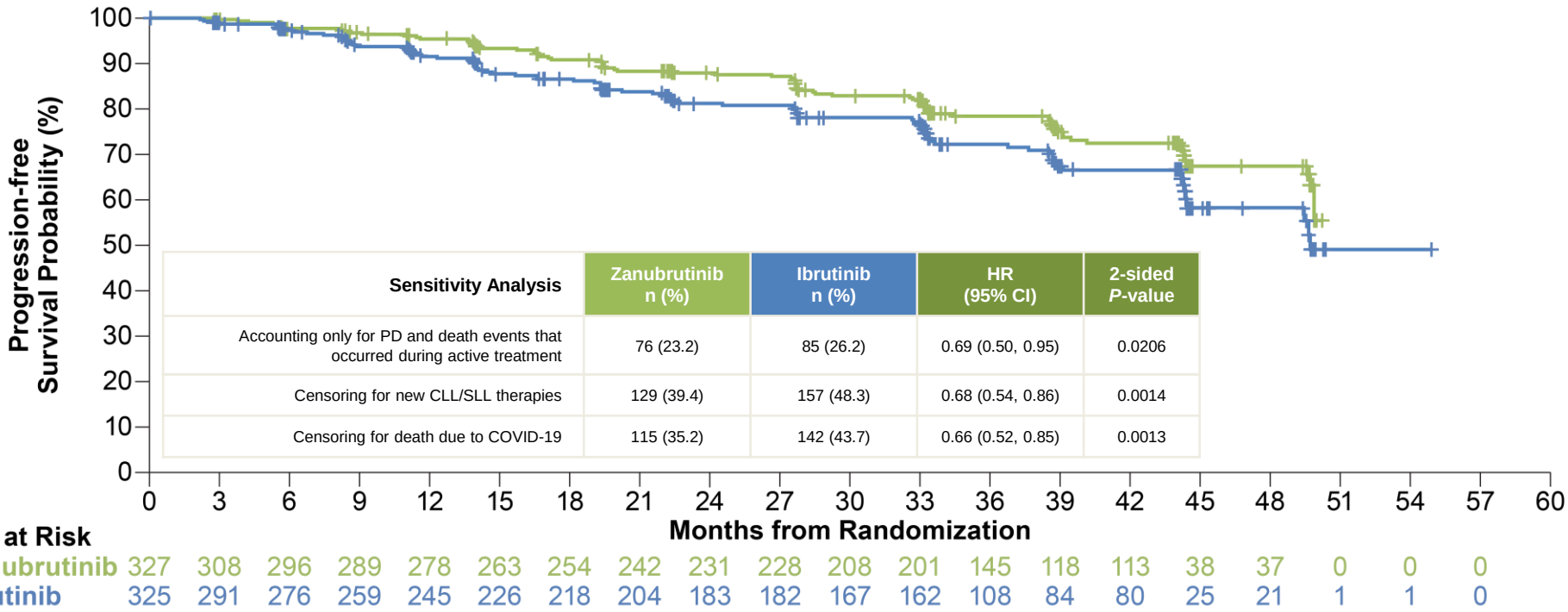


No. at Risk

Zanu with del(17p)/*TP53*	75	71	68	66	64	61	55	52	51	49	45	43	30	22	22	6	6	0	0	0
Ibru with del(17p)/*TP53*	75	70	68	59	54	48	45	41	38	36	30	29	16	10	9	2	1	0	0	0
Zanu w/o del(17p)/*TP53*	251	243	233	228	222	211	203	195	191	187	172	163	121	102	96	36	32	0	0	0
Ibru w/o del(17p)/*TP53*	250	235	225	214	204	194	184	171	162	158	152	142	100	82	79	26	21	1	1	0

Data cutoff: 15 Sep 2023.
PFS, progression-free survival.

Zanubrutinib PFS Benefit Was Consistent Across Multiple Sensitivity Analyses



Sensitivity Analysis	Zanubrutinib n (%)	Ibrutinib n (%)	HR (95% CI)	2-sided *P*-value
Accounting only for PD and death events that occurred during active treatment	76 (23.2)	85 (26.2)	0.69 (0.50, 0.95)	0.0206
Censoring for new CLL/SLL therapies	129 (39.4)	157 (48.3)	0.68 (0.54, 0.86)	0.0014
Censoring for death due to COVID-19	115 (35.2)	142 (43.7)	0.66 (0.52, 0.85)	0.0013

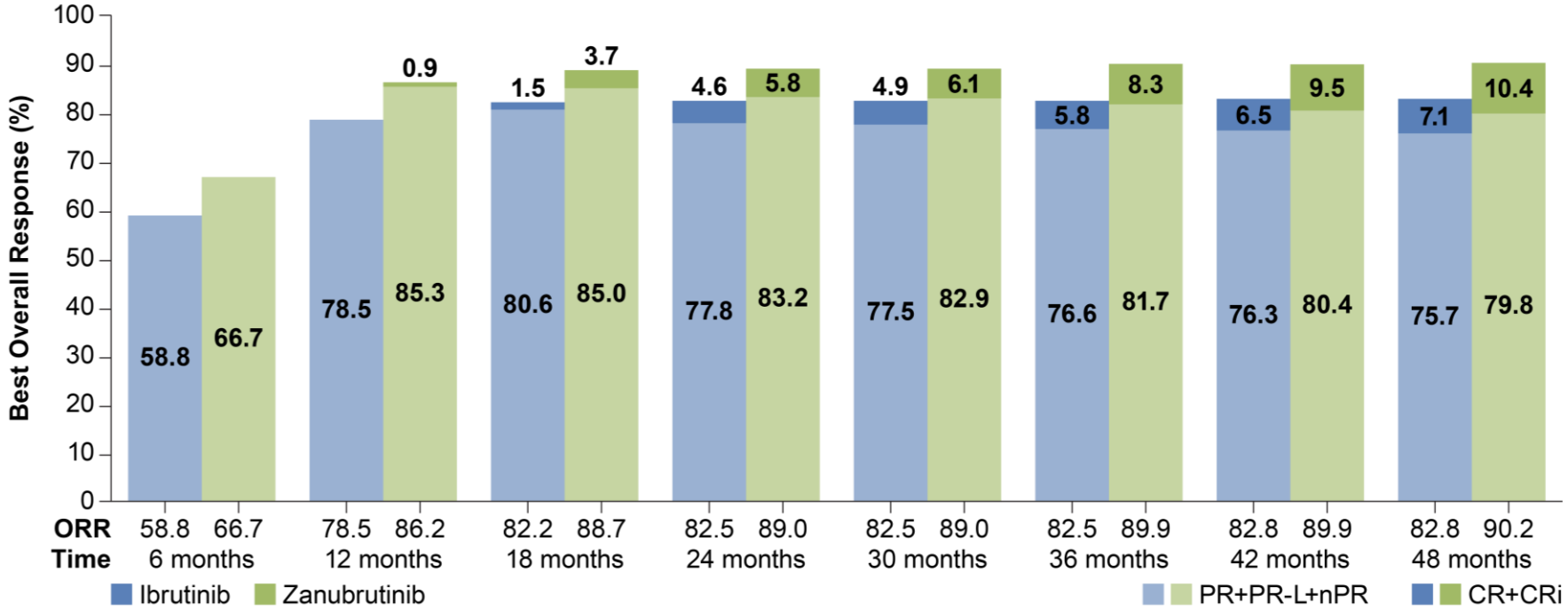
No. at Risk

Zanubrutinib	327	308	296	289	278	263	254	242	231	228	208	201	145	118	113	38	37	0	0	0
Ibrutinib	325	291	276	259	245	226	218	204	183	182	167	162	108	84	80	25	21	1	1	0

Data cutoff: 15 Sep 2023.
PFS, progression-free survival.

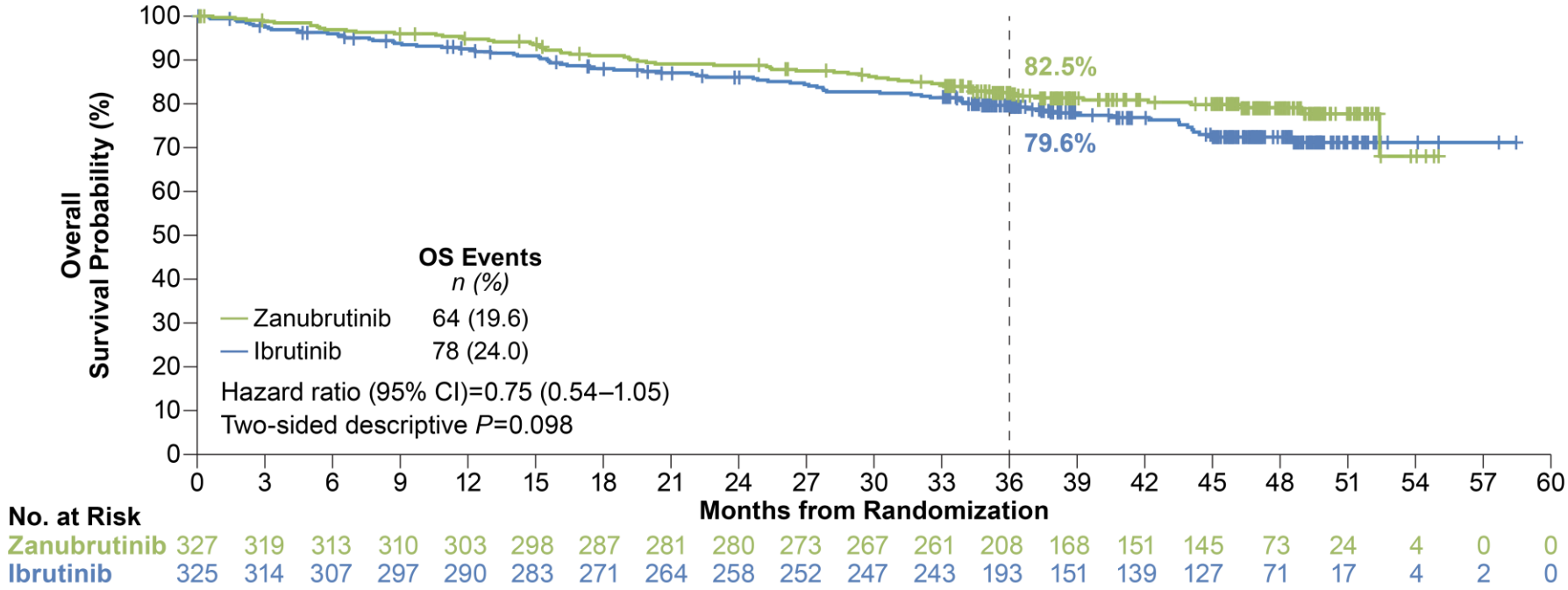
Complete Responses Deepen Over Time in Both Arms

- A higher proportion of patients achieved CR/CRi with zanubrutinib than ibrutinib



Data cutoff: 15 Sep 2023.
CR, complete response; CRi, complete response with incomplete hematologic recovery; ORR, objective response rate; PR, partial response; PR-L, partial response with lymphocytosis; nPR, nodular partial response.

Overall Survival at Longer Follow-up



Data cutoff: 15 Sep 2023.
OS, overall survival.

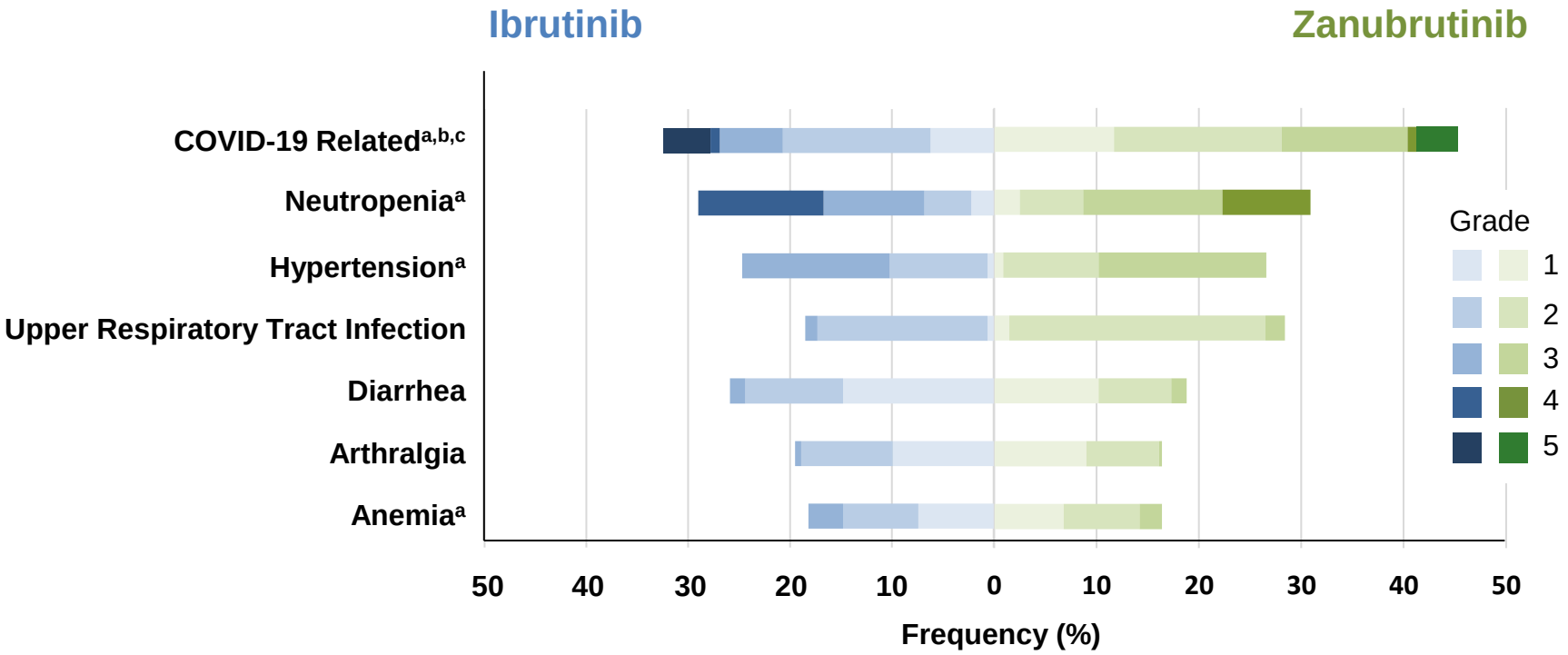
Overall Safety/Tolerability Summary

- Zanubrutinib safety profile remained favorable vs ibrutinib

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Median treatment duration, months	**38.3 (0.4, 54.9)**	**35.0 (0.1, 58.4)**
Any grade adverse event	**320 (98.8)**	**323 (99.7)**
Grade 3 to 5	**235 (72.5)**	**251 (77.5)**
Grade 5	41 (12.7)	40 (12.3)
Serious adverse event	**165 (50.9)**	**191 (59.0)**
Adverse events leading to		
Dose reduction	**47 (14.5)**	**59 (18.2)**
Dose interruption	196 (60.5)	201 (62.0)
Treatment discontinuation	**64 (19.8)**	**85 (26.2)**
Hospitalization	**150 (46.3)**	**180 (55.6)**

Data cutoff: 15 Sep 2023.

Most Common Adverse Events by Grade Occurring in ≥15% of Patients in Both Arms



Data cutoff: 15 Sep 2023.

[a] Pooled MedDRA preferred terms. [b] Includes preferred terms of COVID-19, COVID-19 pneumonia, and suspected COVID-19. [c] Grade 5 COVID-related events: 13 (4.0%) with zanubrutinib and 15 (4.6%) with ibrutinib.

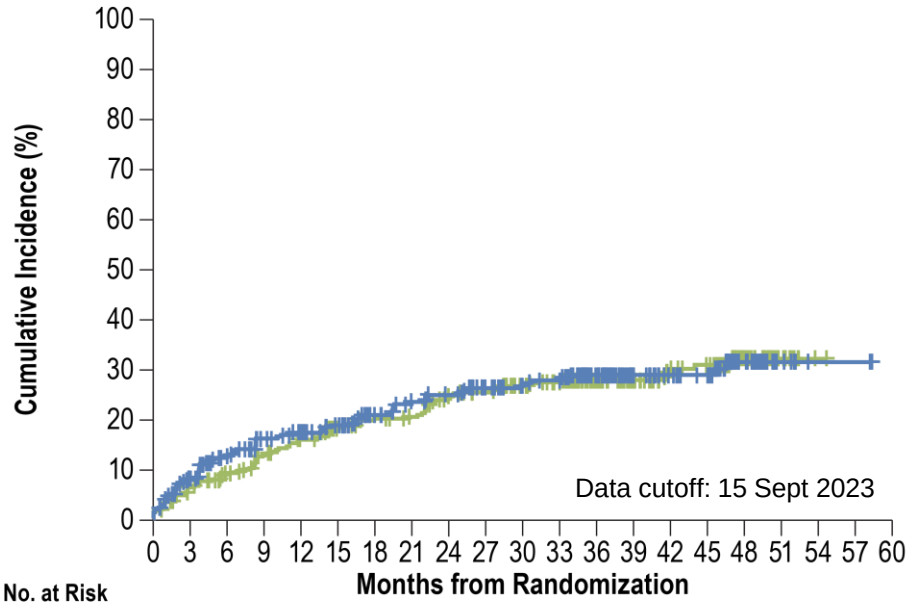
Adverse Events of Special Interest[a] Occurring in ≥2 Patients

	Zanubrutinib (n=324)		Ibrutinib (n=324)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infection	264 (81.5)	115 (35.5)	260 (80.2)	111 (34.3)
Opportunistic Infections	8 (2.5)	6 (1.9)	13 (4.0)	5 (1.5)
COVID-19 Related[b]	**145 (44.8)**	**56 (17.3)**	**105 (32.4)**	**38 (11.7)**
Bleeding	142 (43.8)	12 (3.7)	144 (44.4)	13 (4.0)
Major Hemorrhage	13 (4.0)	12 (3.7)	16 (4.9)	13 (4.0)
Hypertension	**86 (26.5)**	**53 (16.4)**	**80 (24.7)**	**47 (14.5)**
Atrial fibrillation/flutter	**22 (6.8)**	**10 (3.1)**	**53 (16.4)**	**16 (4.9)**
Anemia	53 (16.4)	7 (2.2)	59 (18.2)	11 (3.4)
Neutropenia	**100 (30.9)**	**72 (22.2)**	**94 (29.0)**	**72 (22.2)**
Thrombocytopenia	43 (13.3)	12 (3.7)	53 (16.4)	19 (5.9)
Second primary malignancies	46 (14.2)	26 (8.0)	52 (16.0)	19 (5.9)

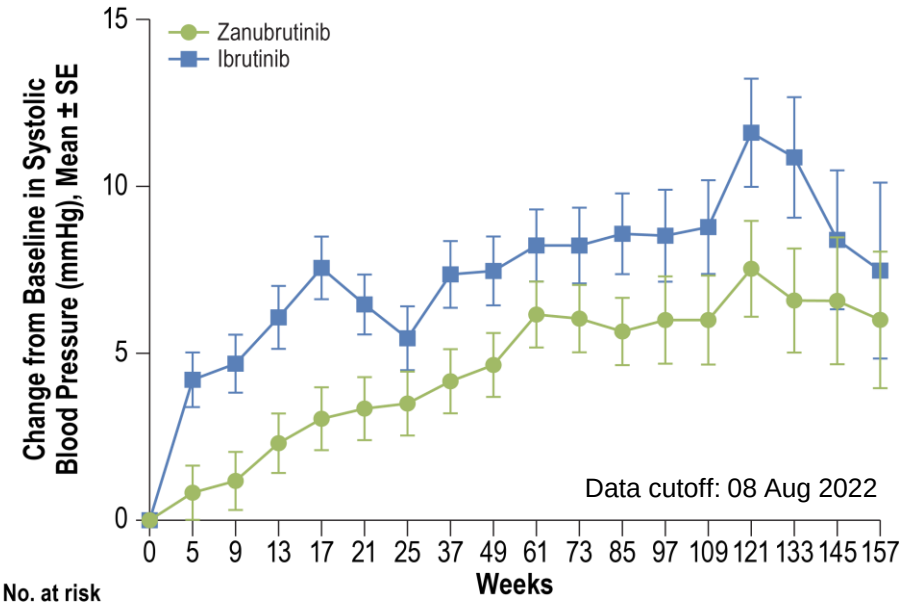
Data cutoff: 15 Sep 2023.

[a] Pooled MedDRA preferred terms. [b] Includes preferred terms of COVID-19, COVID-19 pneumonia, and suspected COVID-19.

Despite Similar Hypertension Rates, Change in Systolic Blood Pressure Was Lower With Zanubrutinib



No. at Risk																				
Zanubrutinib	324	296	279	262	247	232	220	215	196	188	175	165	133	108	91	86	37	10	1	0	0
Ibrutinib	324	280	253	231	221	207	185	172	164	150	140	136	108	79	69	64	32	7	2	2	0



No. at risk																				
Zanubrutinib	327	316	317	314	308	298	295	298	288	281	267	268	231	191	164	150	114	51		
Ibrutinib	325	317	311	301	293	279	278	268	255	248	230	223	190	145	124	112	93	42		

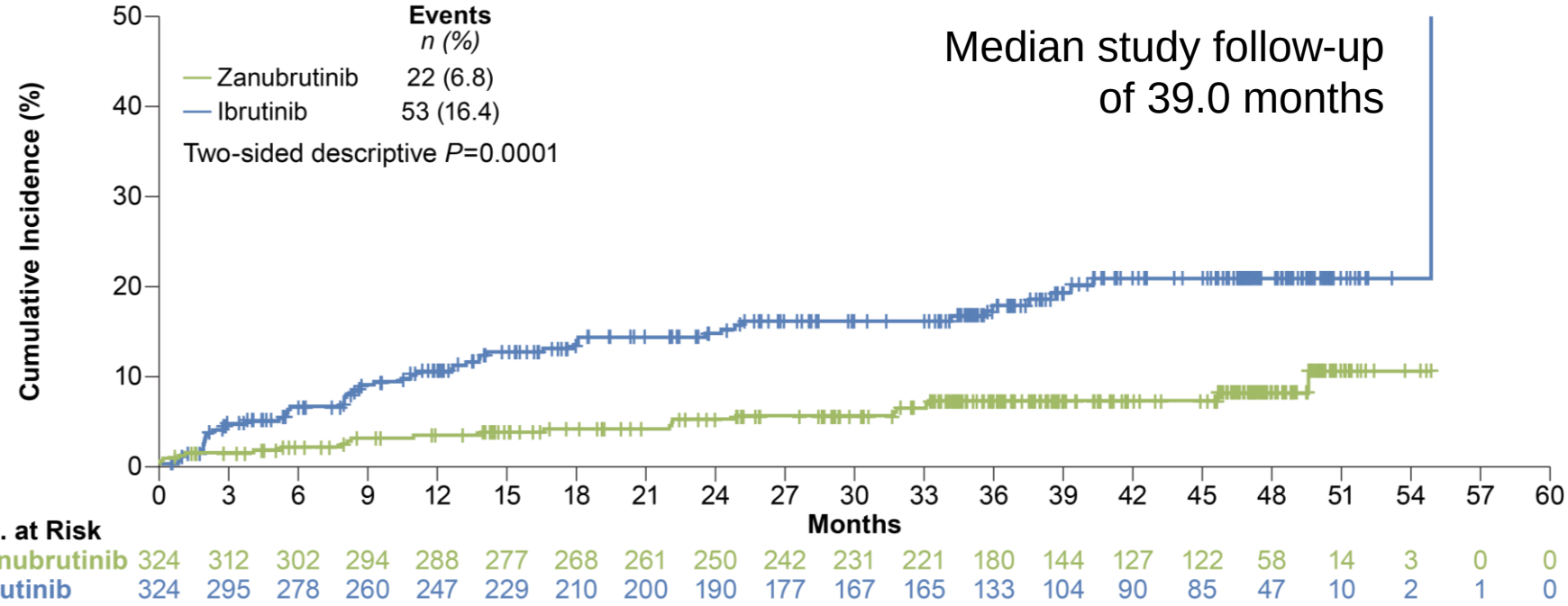
Zanubrutinib Continues to Demonstrate a More Favorable Cardiac Safety Profile Than Ibrutinib

- Serious cardiac adverse events were lower with zanubrutinib vs ibrutinib
  - Atrial fibrillation/flutter (3 vs 13)
  - Ventricular fibrillation (0 vs 2)
  - MI[a]/acute coronary syndrome (3 vs 3)
- **Fatal cardiac events[b]:**
  - **Zanubrutinib, n=0 (0%)**
  - **Ibrutinib, n=6 (1.9%)**

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac adverse events	**80 (24.7)**	**112 (34.6)**
Serious cardiac adverse events	**11 (3.4)**	**31 (9.6)**
Cardiac adverse events leading to treatment discontinuation	**3 (0.9)**	**15 (4.6)**
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation/flutter	1 (0.3)	6 (1.9)
Cardiac failure	1 (0.3)	2 (0.6)
Cardiac arrest	0	2 (0.6)[b]
Cardiac failure acute	0	1 (0.3)[b]
Congestive cardiomyopathy	0	1 (0.3)[b]
Myocardial infarction	0	1 (0.3)[b]
Palpitations	0	1 (0.3)
Ventricular fibrillation	0	1 (0.3)

Data cutoff: 15 Sep 2023.
[a] Including acute MI. [b] Fatal cardiac event (n=6); 1 death (myocardial infarction with ibrutinib) was not listed due to discontinuation due to diarrhea 14 days prior to the fatal event.
MI, myocardial infarction.

Significantly Fewer Atrial Fibrillation/Flutter Events With Zanubrutinib Than Ibrutinib



Data cutoff: 15 Sep 2023.

Conclusions

- ALPINE is the only study to demonstrate PFS superiority in a head-to-head comparison of BTK inhibitors
- Zanubrutinib demonstrated sustained PFS benefit over ibrutinib in patients with R/R CLL/SLL with a median follow-up of 39 months
  - Durable PFS benefits seen across major subgroups, including the del(17p)/*TP53*^{mut} population
  - PFS benefit is consistent across multiple sensitivity analyses demonstrating that PFS advantage with zanubrutinib was primarily driven by efficacy and not tolerability
- While responses deepened over time in both arms, ORR was higher with zanubrutinib with increased rates of CR/CRi compared with ibrutinib
- Zanubrutinib continues to demonstrate a more favorable safety/tolerability profile compared with ibrutinib
  - Lower rate of grade ≥3 and serious AEs, fewer AEs leading to treatment discontinuation, hospitalization, and dose reduction
  - Safer cardiac profile than ibrutinib with significantly lower rates of atrial fibrillation, serious cardiac events, cardiac events leading to treatment discontinuation, and no fatal cardiac events
- **With over 3 years of follow-up, these data reconfirm zanubrutinib improved efficacy over ibrutinib and a more favorable safety profile in patients with R/R CLL/SLL**

AE, adverse event; BTK, Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia or small lymphocytic lymphoma; CR, complete response; CRi, complete response with incomplete hematologic recovery; ORR, objective response rate; PFS, progression-free survival, R/R, relapsed or refractory.

The authors would like to thank the investigators, site support staff, and especially the **patients** and their caregivers for participating in the ALPINE study

Ting, Stephen
Opat, Stephen
Marlton, Paula
Leahy, Michael
Hourigan, Matthew
Janowski, Wojt
Walker, Patricia

Lemmens, Jan

Hu, Jianda
Weng, Jianyu
Zhou, Keshu
Xu, Wei
Feng, Ru
Zhang, Wei
Gao, Sujun

Pan, Ling
Liu, Peng
Hu, Yu
Zhang, Huilai
Jing, Hongmei
Yu, Kang
Jin, Jie

Wang, Zhao
Zhu, Xiongpeng
Wang, Tingyu
Liu, Zhuogang
Li, Ping

Hajek, Roman
Simkovic, Martin
Turcsanyi, Peter
Mayer, Jiri

Ferrant, Emanuelle
Laribi, Kamel
Gruchet, Cecile
Dartigeas, Caroline
Villemagne, Bruno
Bareau, Benoit

Eichhorst, Barbara
Wehler, Thomas

Levin, Mark-David
Schaar, Cornelis

Ghia, Paolo
Frustaci, Anna Maria
Laurenti, Luca
Coscia, Marta

Turgut, Burhan

Hughes, Marie
Elinder Camburn
Weinkove, Robert
Islam, Shahid
Liang, James
Ganly, Peter

Juliusson, Gunnar
Palma, Marzia

Jurczak, Wojciech
Robak, Tadeusz
Holojda, Jadwiga
Krzanowski, Jacek
Ciepluch, Hanna
Mital, Andrzej
Grosicki, Sebastian
Kazmierczak, Maciej
Piszcz, Jaroslaw

Garcia Velva, Jose Antonio
Abril Sabater, Laura
Casado Montero, Luis Felipe
Lopez Jimenez, Javier
Yanez San Segundo, Lucrecia
Baltasar, Patricia
Francesc, Bosch
Argüello, Miguel
Magnano Mayer, Laura
Roncero, Josep

Hutchinson, Claire
Munir, Talha
Forconi, Francesco
Shah, Nimish
Martinez De La Calle, Nicolas
Marshall, Scott
Walewska, Renata
Paneesha, Shankaranarayana
Preston, Gavin
Young, Moya

Brown, Jennifer
Flinn, Ian
Kingsley, Edwin
Shadman, Mazyar
Quick, Donald
Brander, Danielle
Yimer, Habte
Ferrajoli, Alessandra
Spurgeon, Stephen
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

Additionally, we would like to thank the BeiGene ALPINE study team for all their efforts and hard work.
Slide development, under the direction of the authors, was provided by Regina Switzer, PhD, Yin Lin, PhD, Nathan McCance, BFA, and Elizabeth Hermans, PhD.