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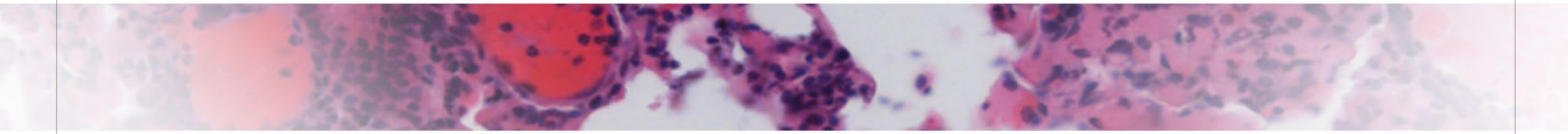

Extended Follow-up of ALPINE Randomized Phase 3 Study Confirms Sustained Superior Progression-free Survival of Zanubrutinib Versus Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (R/R CLL/SLL)

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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

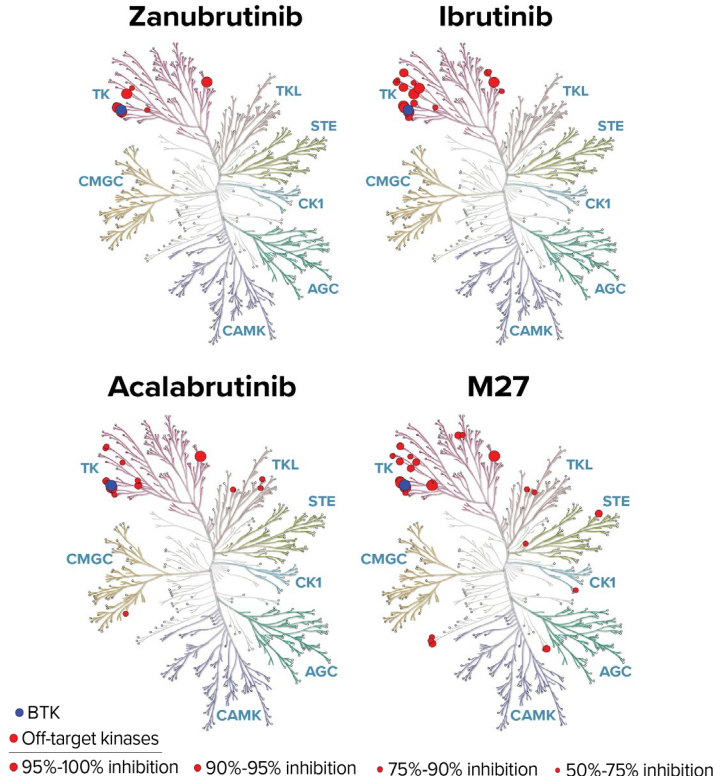


Figure adapted from Shadman et al. *Lancet Haematol.* 2023.

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

ALPINE Study Design (NCT03734016)

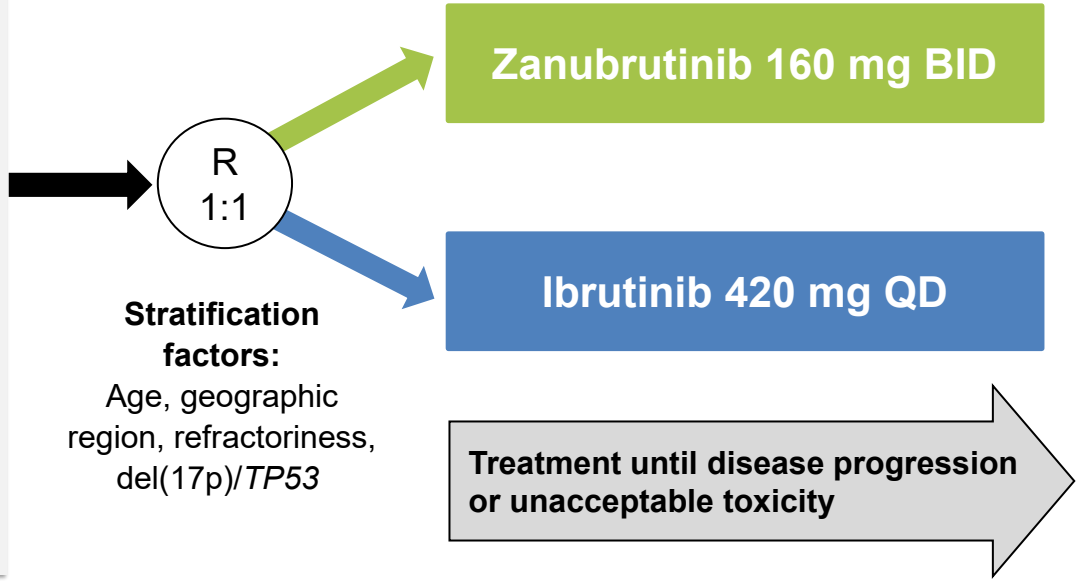
R/R CLL/SLL with ≥1 prior treatment
(N=652)

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.

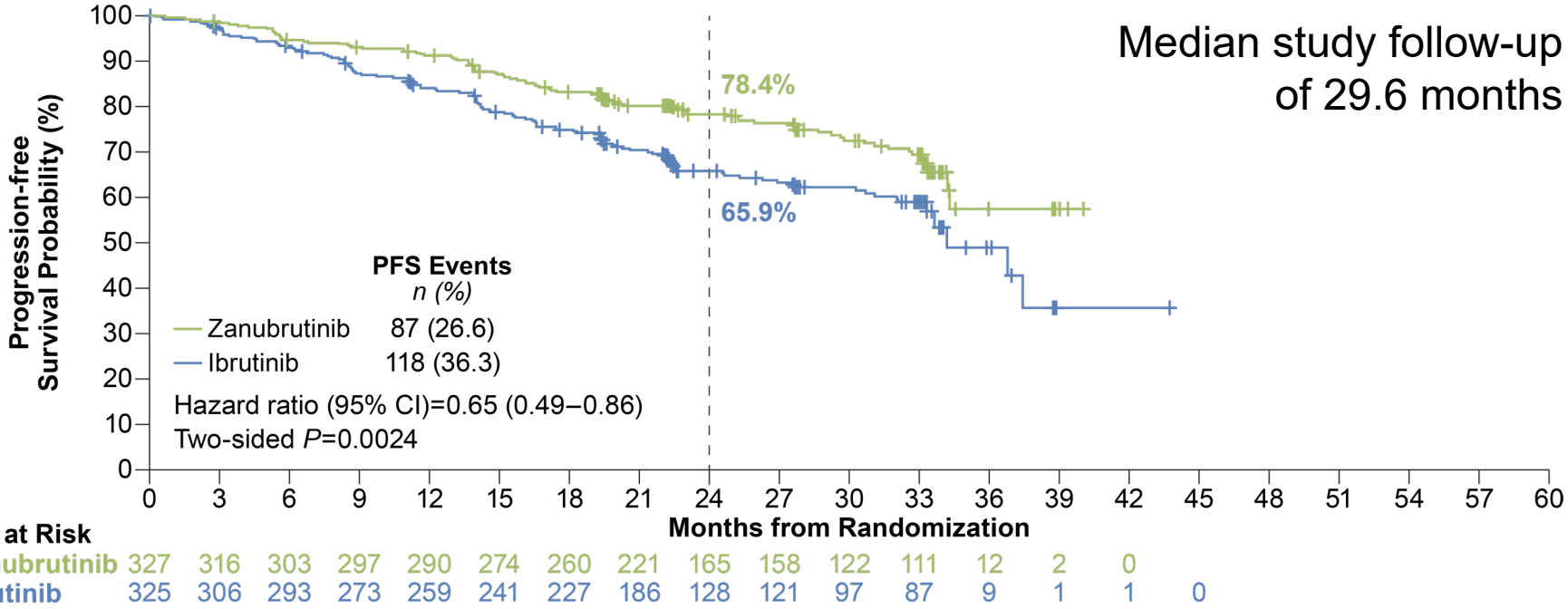
Balanced Demographics and Disease Characteristics

	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)**

[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.

Previous Report Demonstrated Zanubrutinib is Clinically and Statistically Superior to Ibrutinib



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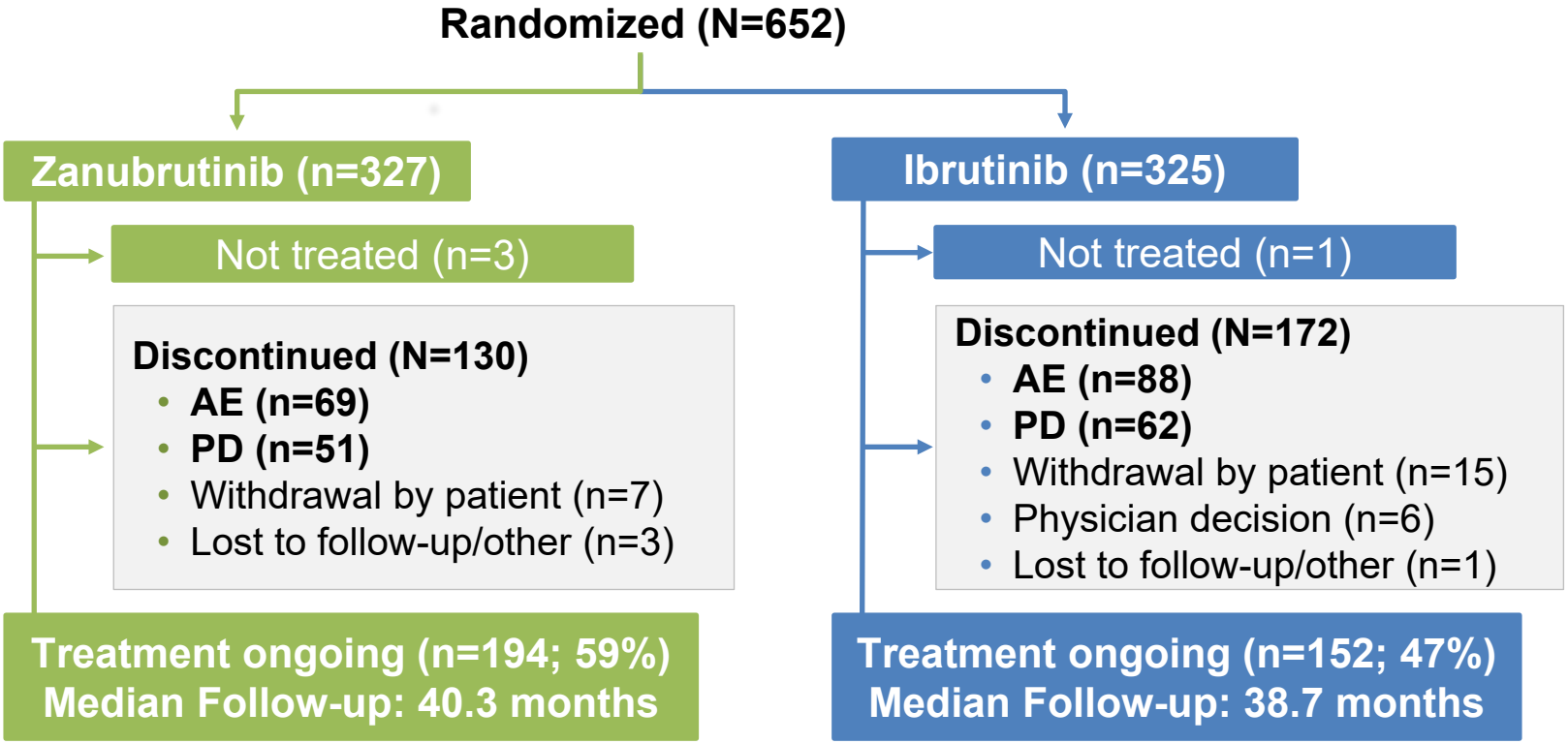
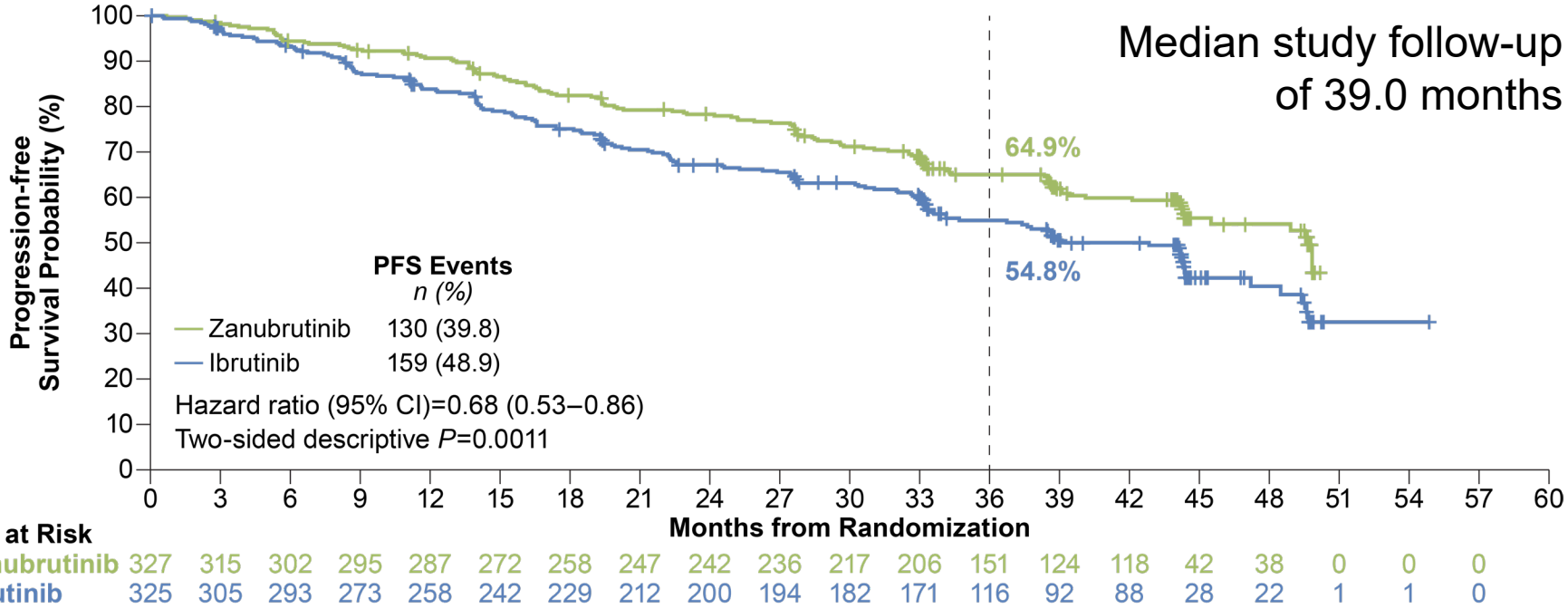
Patient Disposition at Extended Follow-up



Data cutoff: 15 Sep 2023

Zanubrutinib Sustains PFS Benefit Over Ibrutinib At Extended Follow-up



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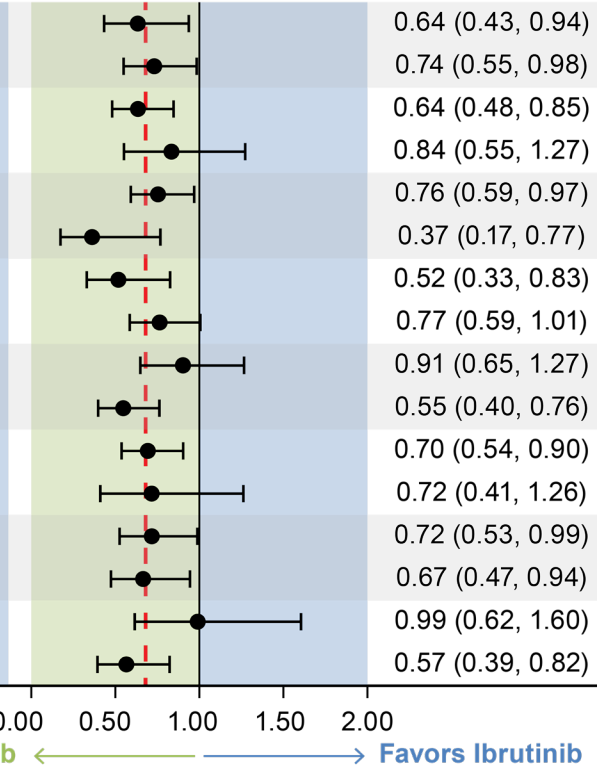
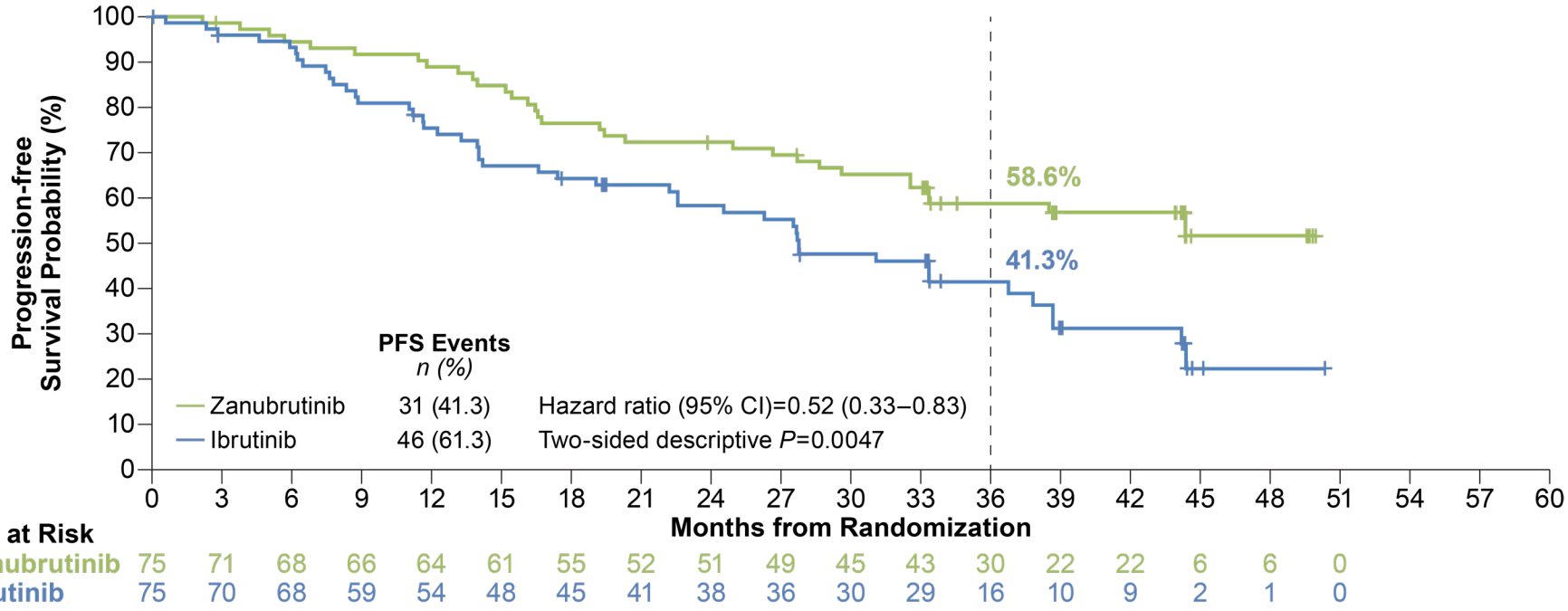
PFS Favored Zanubrutinib Across Subgroups

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)

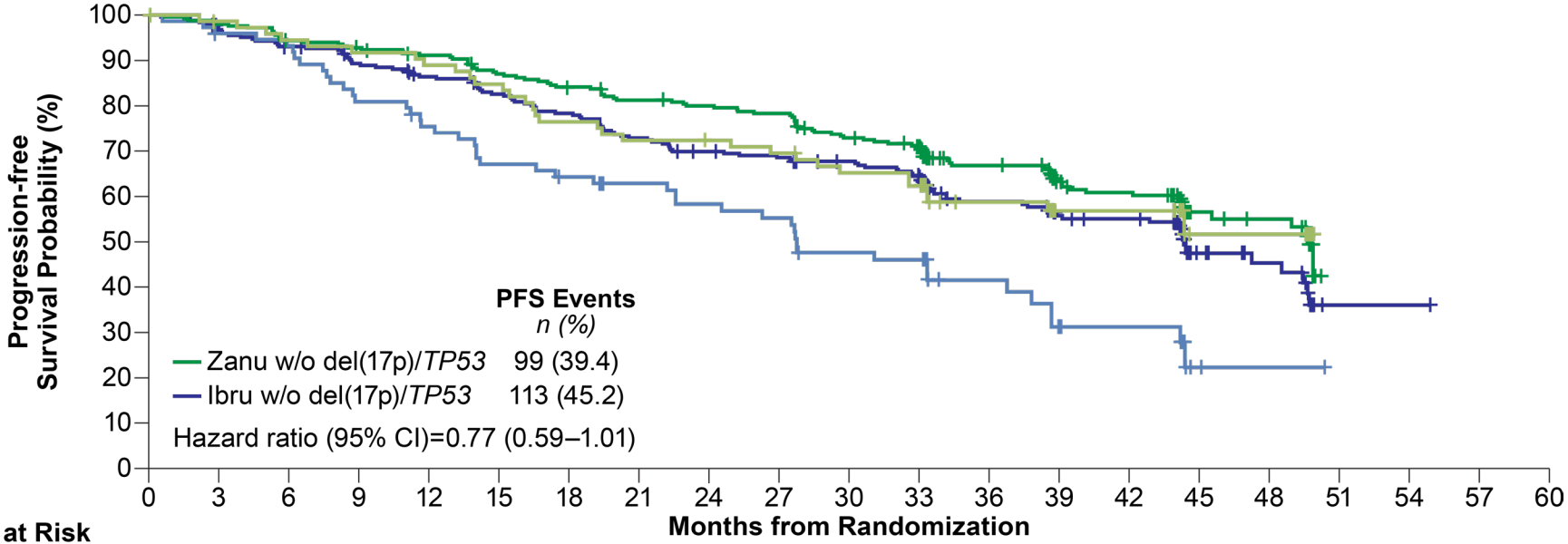


[a]Hazard ratio and 95% confidence interval were unstratified for subgroups.

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



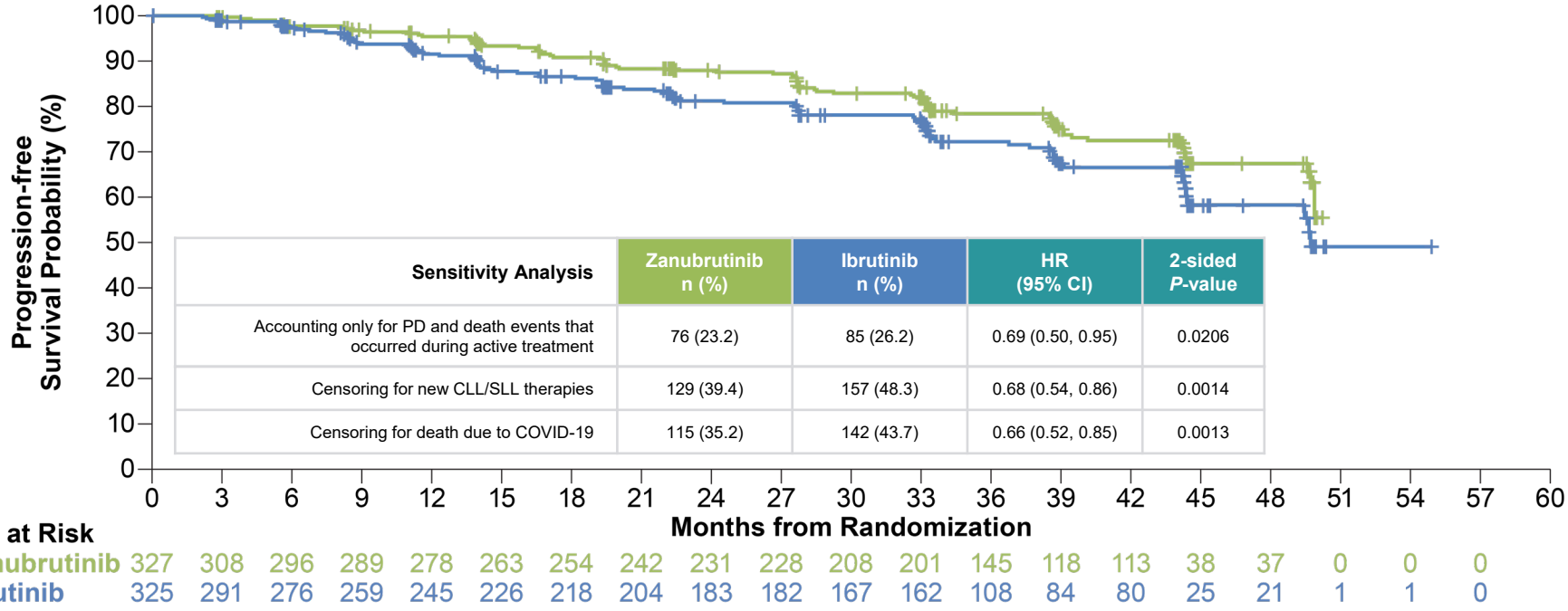
Zanubrutinib Demonstrated Robust PFS Benefit Independent of del(17p)/*TP53* Mutation Status



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

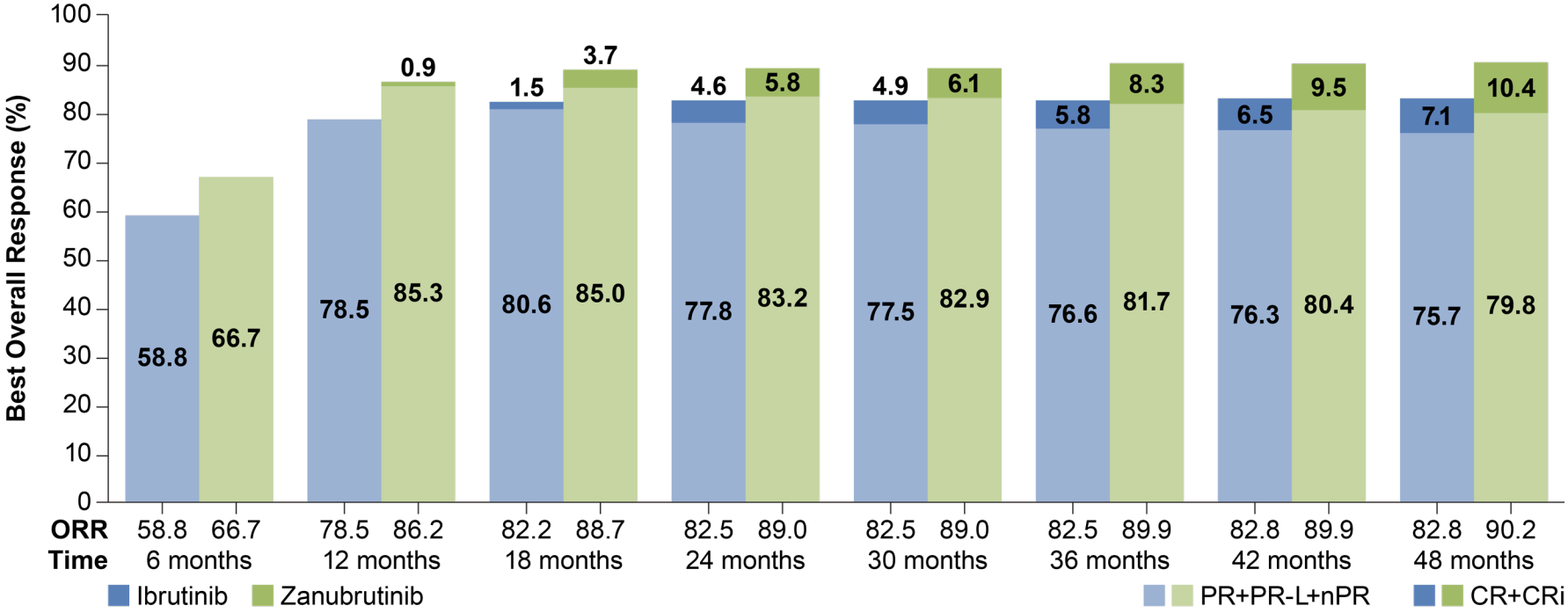
Zanubrutinib PFS Benefit Was Consistent Across Multiple Sensitivity Analyses



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

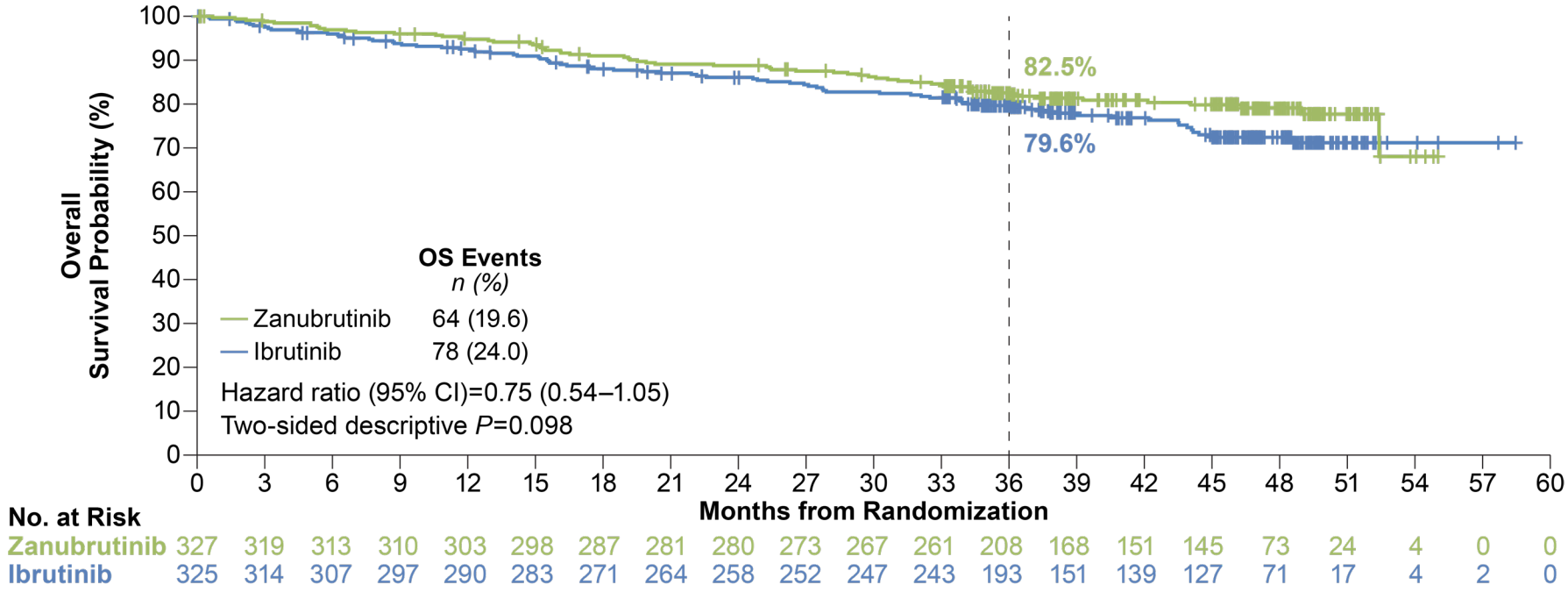
Complete Responses Deepen Over Time in Both Arms

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



Data cutoff: 15 Sep 2023

Overall Survival at Longer Follow-up



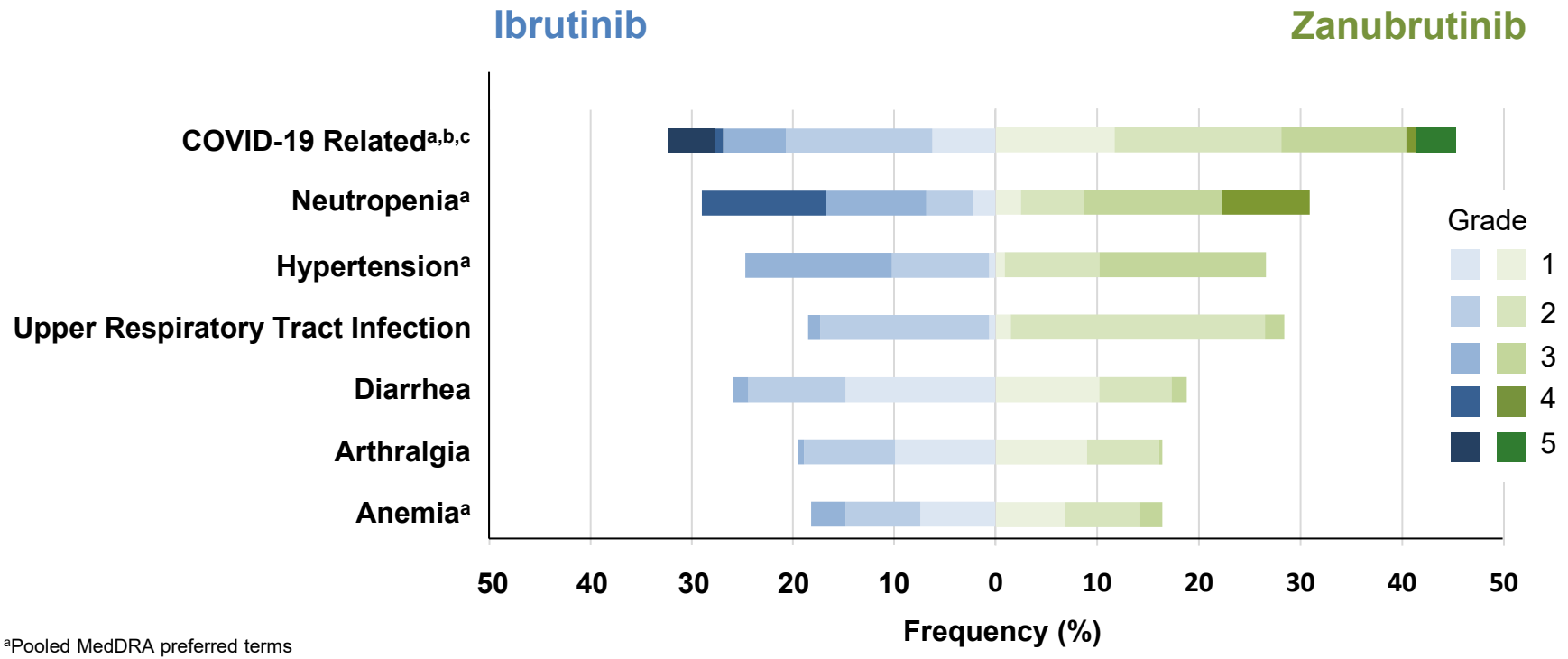
Data cutoff: 15 Sep 2023

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)**

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



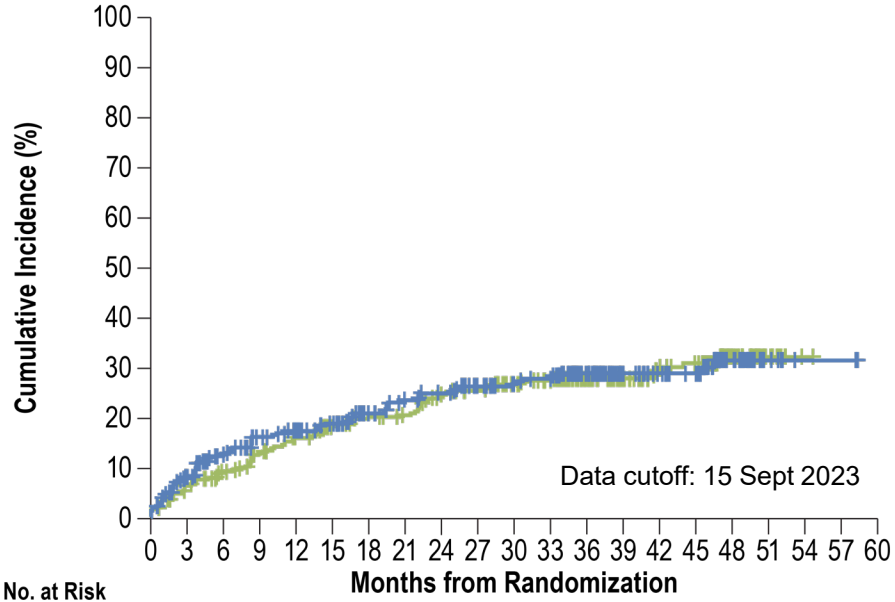
[a]Pooled MedDRA preferred terms
[b]Includes preferred terms of COVID-19, COVID-19 pneumonia, and suspected COVID-19.
[c]Grade 5 COVID-related events: 13 (4.0%) with zanubrutinib and 15 (4.6%) with ibrutinib.

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)

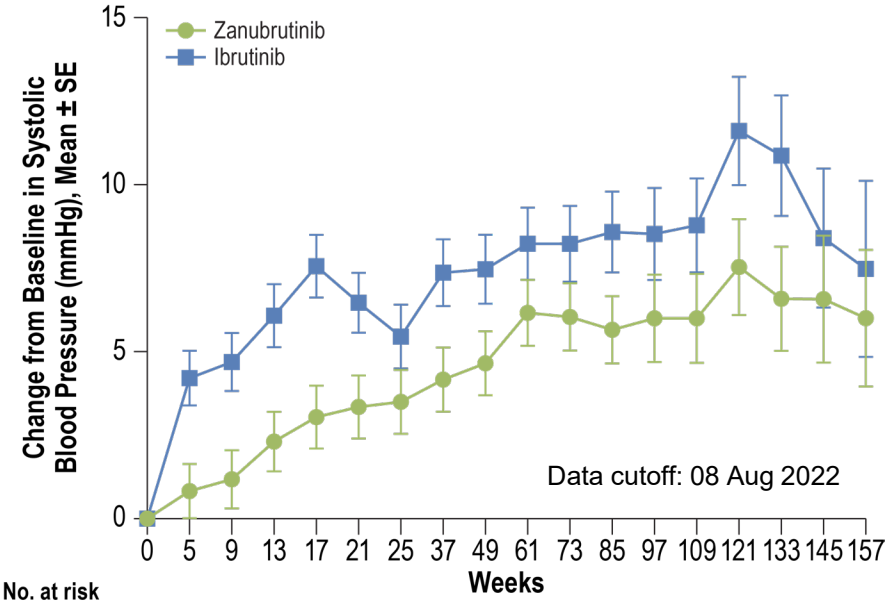
[a]Pooled MedDRA preferred terms.
[b]Includes preferred terms of COVID-19, COVID-19 pneumonia, and suspected COVID-19.

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)

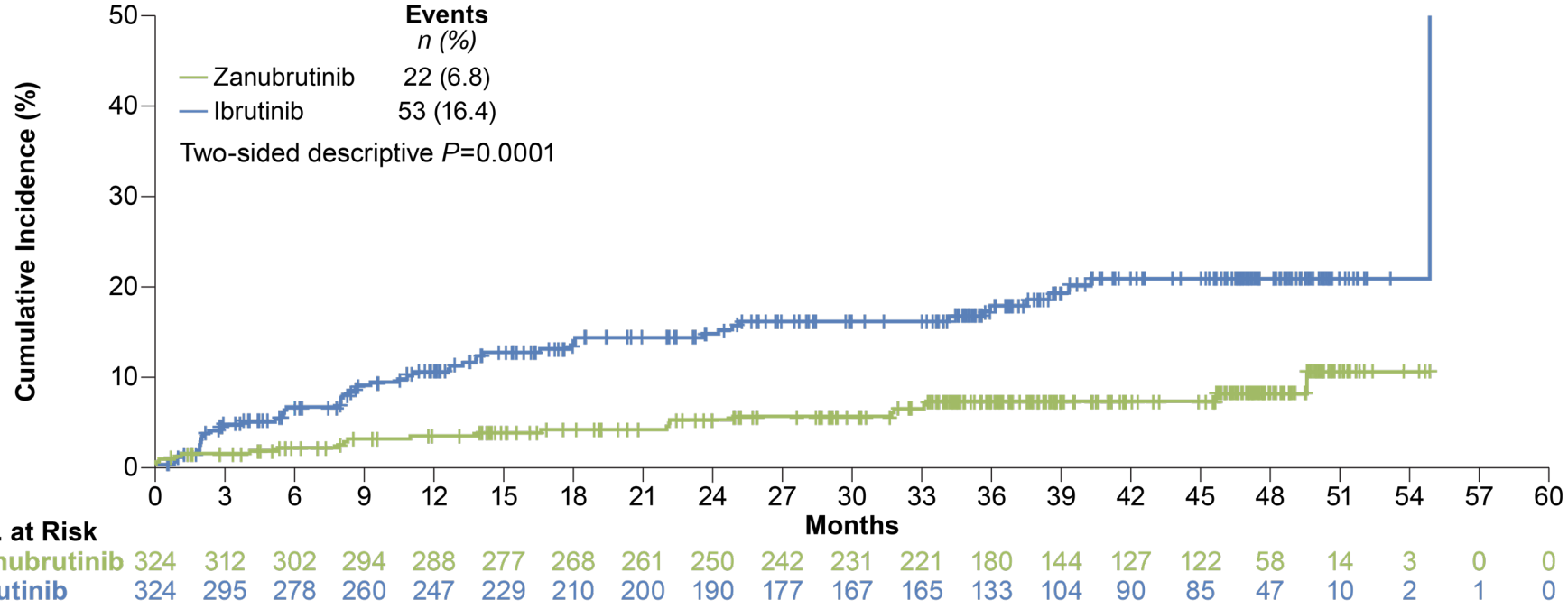
[a]Including acute MI.

[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.

Abbreviations: MI, myocardial infarction.

Data cutoff: 15 Sep 2023

Significantly Fewer Atrial Fibrillation/Flutter Events With Zanubrutinib Than Ibrutinib



Median study follow-up 39.0 months

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, 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**

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

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