ALPINE

ALPINE Trial Design

Phase 3

Study Identifier:
BGB-3111-305, NCT03734016

Primary Endpoint: ORR
Key Secondary Endpoints: PFS, OS, safety

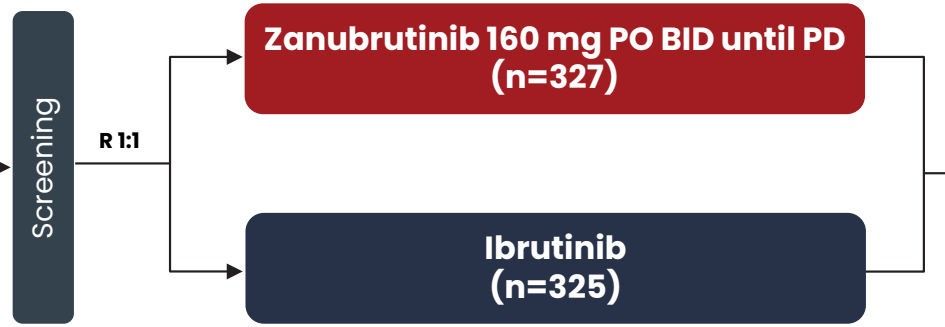
Key eligibility criteria

- R/R CLL/SLL requiring treatment
- Measurable disease by CT/MRI
- No current or past history of Richter's transformation
- No prior treatment with a BTK inhibitor

Stratification factors

- Age (<65 vs ≥65 years)
- China vs ex-China
- Refractory status (yes/no)
- del(17p)/*TP53* (present vs absent)

Treatment



Follow-up

Safety and survival

BID=twice daily, BTK=Bruton tyrosine kinase, CLL=chronic lymphocytic leukemia, CT=computed tomography, MRI=magnetic resonance imaging, ORR=objective response rate, OS=overall survival, PD=progressive disease, PFS=progression-free survival, PO=per oral, QD=once daily, R=randomized, R/R=relapsed/refractory, SLL=small lymphocytic lymphoma.

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03734016. Accessed October 9, 2025.; 2. Hillmen P, et al. *J Clin Oncol*. 2023;41:1035-1045; 3. Brown JR et al. *Blood*. 2024; ePub ahead of print.

ALPINE

Patient Demographics and Disease Characteristics

	Zanubrutinib (N=327)	Ibrutinib (N=325)
Age, median (range)	67 (35-90)	68 (35-89)
Male	213 (65.1)	232 (71.4)
ECOG PS ≥1, n (%)	198 (60.6)	203 (62.5)
Race, n (%)		
White	261 (79.8)	265 (81.5)
Asian	47 (14.4)	44 (13.5)
Black or African American	4 (1.2)	2 (0.6)
Native Hawaiian or Other Pacific Islander	3 (0.9)	0
Multiple	1 (0.3)	0
Other/Not reported/Unknown	11 (3.4)	14 (4.3)
Prior lines of systemic therapy, median (range)	1 (1-6)	1 (1-12)
>3 prior lines, n (%)	24 (7.3)	30 (9.2)
del(17p) and/or *TP53*^{mut}, n (%)	75 (22.9)	75 (23.1)
del(17p)	45 (13.8)	50 (15.4)
TP53^{mut} without del(17p)	30 (9.2)	25 (7.7)

	Zanubrutinib (N=327)	Ibrutinib (N=325)
IGHV mutational status, n (%)		
Mutated	80 (24.5)	70 (21.5)
Unmutated	240 (73.4)	241 (74.2)
Missing	7 (2.1)	14 (4.3)
Complex karyotype[a] (%) (≥3 abnormalities)		
Yes	56 (17.1)	70 (21.5)
No	153 (46.8)	130 (40.0)
Missing	118 (36.1)	125 (38.5)
Complex karyotype[a] (%) (≥5 abnormalities)		
Yes	32 (9.8)	38 (11.7)
No	177 (54.1)	162 (49.8)
Missing	118 (36.1)	125 (38.5)
Bulky disease (≥5 cm), n (%)	145 (44.3)	149 (45.8)

Data cutoff: February 28, 2024.
[a]Centrally assessed.
ECOG PS=Eastern Cooperative Oncology Group performance status, IGHV=immunoglobulin heavy chain variable.
Brown JR et al. *Blood*. 2024;144:2706-2717.

ALPINE

Primary Endpoint: Investigator-Assessed ORR

At the prespecified interim analysis (median follow-up: 15.3 months), zanubrutinib had a superior overall response rate than ibrutinib (78.3% vs 62.5%, two-sided *P=0.0006*)[1]

Best Response, n (%)	All Patients		del(17p)/*TP53*	
	Zanubrutinib (n=207)	Ibrutinib (n=208)	Zanubrutinib (n=41)	Ibrutinib (n=38)
ORR	**162 (78.3)[a]**	**130 (62.5)[a]**	**33 (80.5)**	**19 (50.0)**
95% CI	**72.0, 83.7**	**55.5, 69.1**	**65.1, 91.2**	**33.4, 66.6**
CR or CRi	4 (1.9)	3 (1.4)	0	0
PR or nPR	158 (76.3)	127 (61.1)	33 (80.5)	19 (50)
PR-L	21 (10.1)	39 (18.8)	3 (7.3)	8 (21.1)
SD	17 (8.2)	28 (13.5)	2 (4.9)	8 (21.1)
PD	1 (0.5)	2 (1.0)	0	1 (2.6)
Discontinue before first assessment, NA or NE	6 (2.9)	9 (4.3)	3 (7.3)	2 (5.3)

At a median follow-up of 42.5 months[2]:
ORR was 85.6% with zanubrutinib and 75.4% with ibrutinib

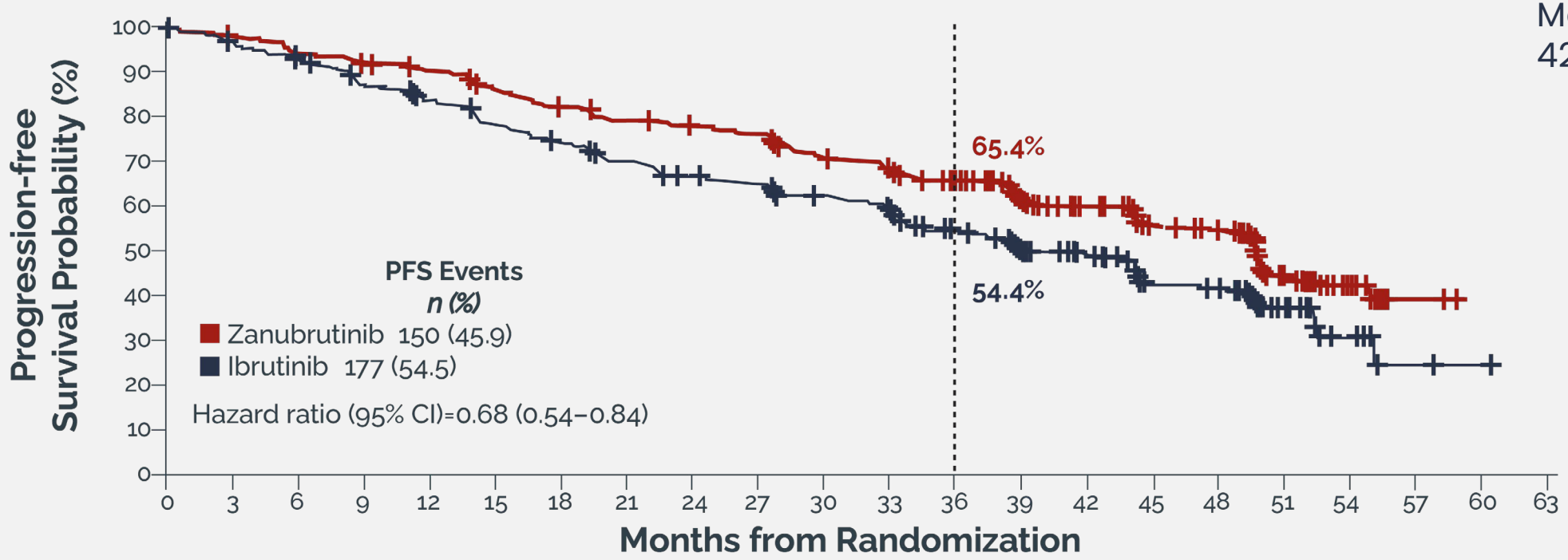
Data cutoff: December 31, 2020.
[a]Noninferiority one-sided *P*<.0001, superiority two-sided *P*=.0006.
CI=confidence interval, CR=complete response, CRi=complete response with incomplete bone marrow recovery, IRC=independent review committee, NA=not assessed, NE=not evaluable, nPR=nodular partial response, ORR=overall response rate, PD=progressive disease, PR=partial response, PR-L=partial response with lymphocytosis, SD=stable disease.
1. Hillmen P et al. *J Clin Oncol*. 2023;41:1035-1045; 2. Brown JR et al. *Blood*. 2024;144:2706-2717.

ALPINE

Progression-Free Survival by Investigator (ITT Population)

At the final PFS analysis (August 8, 2022; median follow-up: 29.6 months), zanubrutinib demonstrated superiority for INV-assessed PFS vs ibrutinib.
At an extended follow-up, zanubrutinib sustained PFS benefit over ibrutinib (figure)

Median follow-up: 42.5 months



No. at Risk																					
Zanubrutinib	327	315	302	295	287	272	258	247	242	236	218	210	189	151	128	109	104	43	19	2	0	0
Ibrutinib	325	305	293	273	258	242	229	212	200	194	183	173	148	116	101	77	74	30	10	2	1	0

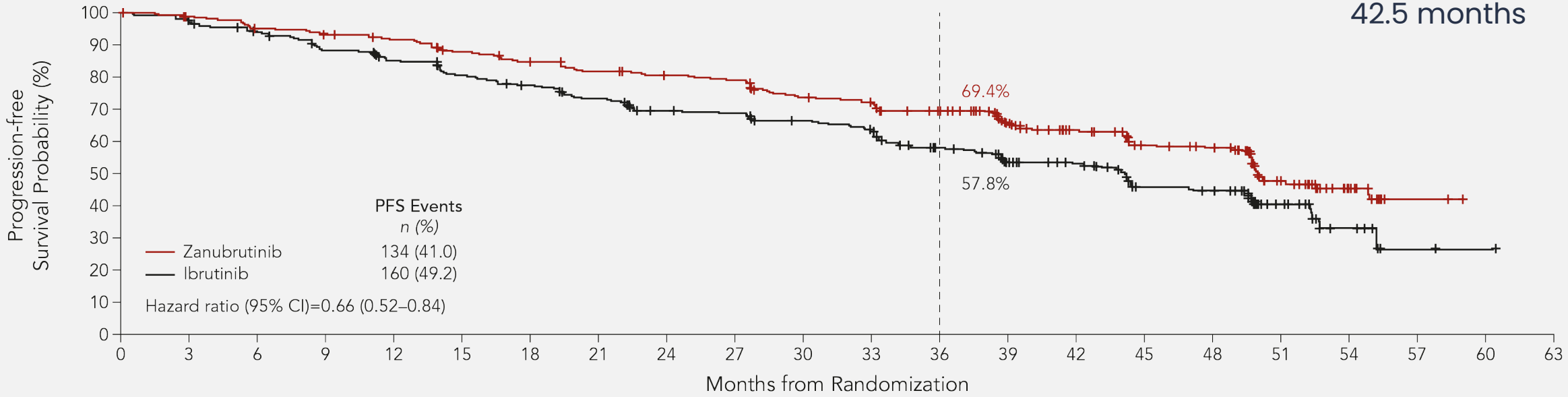
Data cutoff: February 28, 2024.
CI=confidence interval, INV=investigator, PFS=progression-free survival.
Brown JR et al. *Blood*. 2024;144:2706-2717.

ALPINE

Progression-Free Survival by Investigator: COVID-Adjusted

Sensitivity analysis:
Censoring for deaths attributed to COVID-19

Median follow-up: 42.5 months



No. at risk

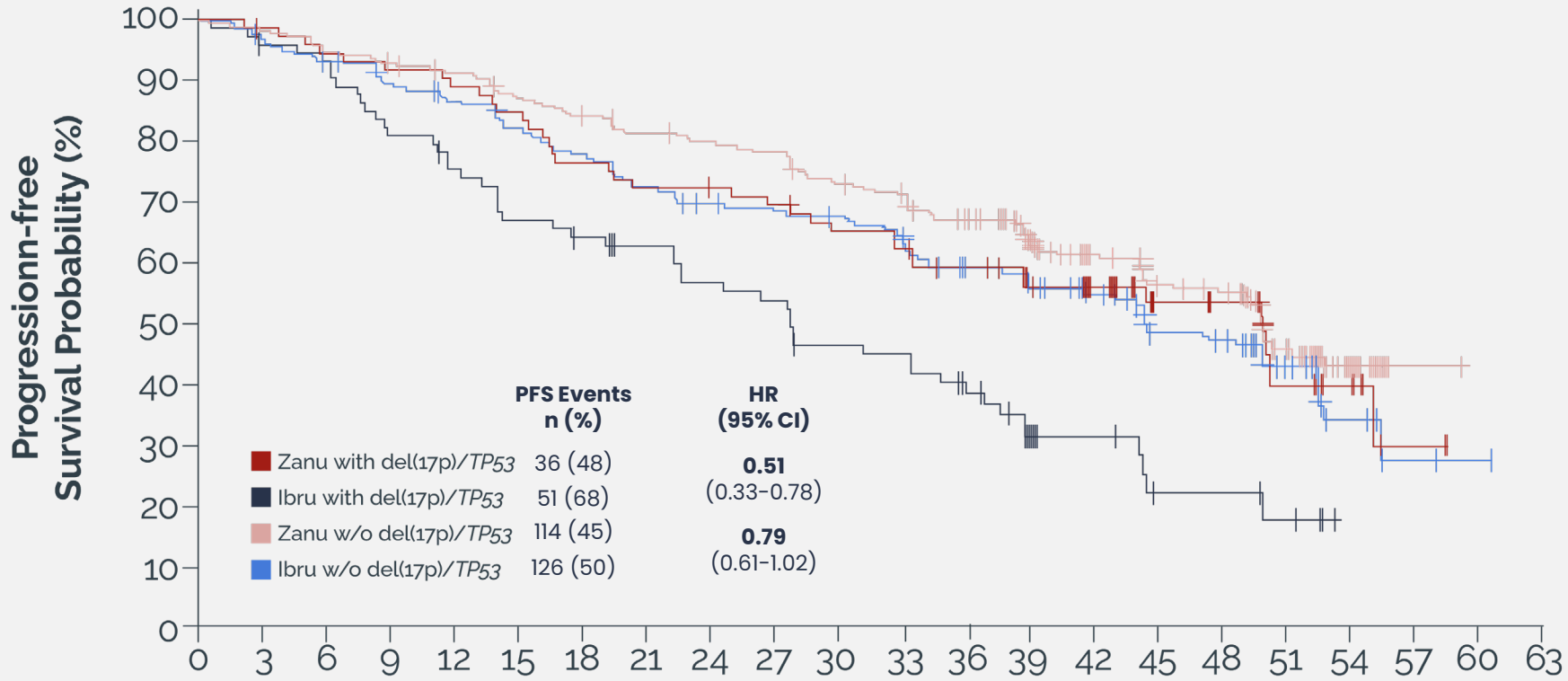
Zanubrutinib	327	313	301	295	286	268	257	247	241	236	214	208	189	151	128	108	103	43	19	2	0	0
Ibrutinib	325	304	292	271	256	238	227	213	197	194	182	173	147	116	101	76	73	30	10	2	1	0

Data cut-off: February 28, 2024.
CI=confidence interval, PFS=progression-free survival.
Brown JR et al. *Blood*. 2024;144:2706-2717.

ALPINE

Exploratory Subgroup Analysis: PFS by del(17p)/*TP53* Mutation Status

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	39	31	25	20	19	8	5	1	0	0
Ibru with del(17p)/*TP53*	75	70	68	59	54	48	45	42	38	36	30	29	23	13	11	6	6	4	0	0	0	0
Zanu w/o del(17p)/*TP53*	251	243	233	228	222	211	203	195	191	187	173	167	150	120	103	89	85	35	14	1	0	0
Ibru w/o del(17p)/*TP53*	250	235	225	214	204	193	183	171	162	158	153	144	125	103	90	71	68	26	10	2	1	0

Median follow-up: 42.5 months

Data cutoff: 28 Feb 2024.
CI=confidence interval, HR=hazard ratio, PFS=progression-free survival.
Brown JR et al. *Blood*. 2024;144:2706-2717.

ALPINE

Most Common AEs and AEs of Special Interest[a]

Zanubrutinib safety profile remained favorable versus ibrutinib

n (%)	Zanubrutinib (n=324)		Ibrutinib (n=324)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infection	266 (82.1)	118 (36.4)	262 (80.9)	115 (35.5)
Opportunistic infections[b]	9 (2.8)	6 (1.9)	14 (4.3)	6 (1.9)
COVID-19 related[c]	**149 (46.0)**	**58 (17.9)**	**108 (33.3)**	**39 (12.0)**
Bleeding	145 (44.8)	12 (3.7)	146 (45.1)	13 (4.0)
Major hemorrhage	13 (4.0)	12 (3.7)	16 (4.9)	13 (4.0)
Hypertension	**88 (27.2)**	**55 (17.0)**	**82 (25.3)**	**52 (16.0)**
Atrial fibrillation/flutter	**23 (7.1)**	**11 (3.4)**	**55 (17.0)**	**17 (5.2)**
Anemia	54 (16.7)	8 (2.5)	60 (18.5)	11 (3.4)
Neutropenia	**102 (31.5)**	**74 (22.8)**	**96 (29.6)**	**74 (22.8)**
Thrombocytopenia	44 (13.6)	13 (4.0)	53 (16.4)	19 (5.9)
Second primary malignancies	46 (14.2)	26 (8.0)	53 (16.4)	19 (5.9)

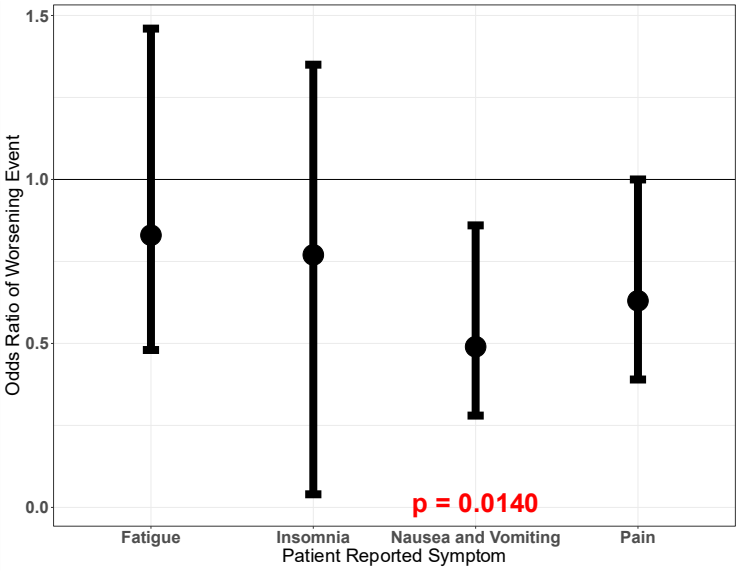
Overall, cardiac events remained lower with zanubrutinib compared with ibrutinib, including the rate of atrial fibrillation.
Fewer zanubrutinib-treated patients discontinued treatment due to AEs.

Data cutoff: February 28, 2024.
[a]Pooled MedDRA preferred terms; [b]Opportunistic infections occurring in ≥2 patients in either arm were fungal pneumonia (zanubrutinib, n=2; ibrutinib, n=4); aspergillosis bronchopulmonary (zanubrutinib, n=2; ibrutinib, n=1); pneumocystis jirovecii pneumonia (zanubrutinib, n=1; ibrutinib, n=2); ophthalmic herpes (zanubrutinib, n=0; ibrutinib, n=2); ophthalmic herpes zoster (zanubrutinib, n=0; ibrutinib, n=2); [c]Includes preferred terms of COVID-19, COVID-19 pneumonia, and suspected COVID-19.
AE=adverse event.
Brown JR et al. *Blood*. 2024;144:2706-2717.

ALPINE

PROs: Symptom-Based Progression-Free Survival

Zanubrutinib Was Associated With Lower Probability of Patient-Reported Symptom Worsening Versus Ibrutinib

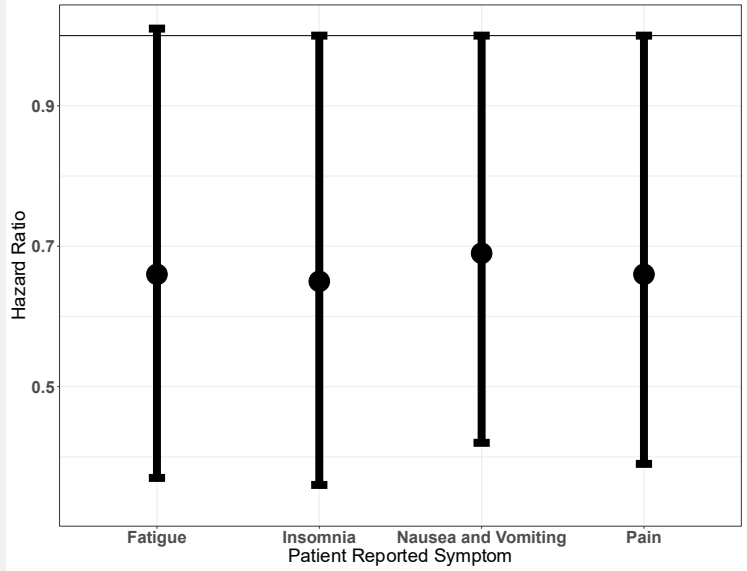


Odds Ratios and 95% Confidence Intervals

Parameter	Fatigue	Insomnia	Nausea and Vomiting	Pain
Zanubrutinib	0.83 (0.48, 1.46)	0.77 (0.44, 1.35)	0.49 (0.28, 0.86)	0.63 (0.39, 1.00)

- Zanubrutinib was significantly associated with lower probability of worsening nausea/vomiting relative to ibrutinib

Patients on Zanubrutinib Showed Lower Risk of Disease Progression Relative to Ibrutinib



Hazard Ratios and 95% Confidence Intervals

Parameter	Fatigue	Insomnia	Nausea and Vomiting	Pain
Zanubrutinib	0.66 (0.37, 1.01)	0.65 (0.36, 1.00)	0.69 (0.42, 1.00)	0.66 (0.39, 1.00)

- Overall risk of PFS is lower in the zanubrutinib versus ibrutinib arm

ORs < 1 indicate that zanubrutinib is protective relative to ibrutinib.
Brown JR, et al. Oral Presentation at ASH 2025;8440.