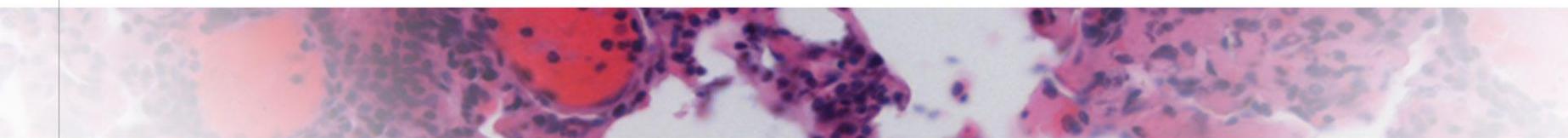




American Society of Hematology
Helping hematologists conquer blood diseases worldwide



Symptom-Based Progression-Free Survival (S-PFS) as a Clinically Relevant and Patient-Centric Endpoint in Chronic Lymphocytic Leukemia (CLL) / Small Lymphocytic Lymphoma (SLL): Results From the ALPINE Trial

Jennifer R Brown,¹ Timothy Victor,^{2,3} Alan Wu,³ Nicole Lamanna,⁴ Constantine S Tam,⁵ Lugui Qiu,⁶ Rasika Korde,³ Tommi Salmi,⁷ Gisoo Barnes,³ Mazyar Shadman^{8,9}

¹Dana-Farber Cancer Institute, Boston, MA, USA; ²University of Pennsylvania, Philadelphia, PA, USA; ³BeOne Medicines Ltd, San Carlos, CA, USA; ⁴Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY, USA; ⁵Alfred Health & Monash University, Melbourne, Victoria, Australia; ⁶State Key Laboratory of Experimental Hematology, National Clinical Medical Research Center for Blood Diseases, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China; ⁷BeOne Medicines Ltd, Switzerland, GmbH, Basel, Switzerland; ⁸Fred Hutchinson Cancer Center, Seattle, WA, USA; ⁹University of Washington, Seattle, WA, USA

Background

- Advancements in BTK inhibitors have reshaped the treatment landscape in CLL/SLL, improving long-term disease control and tolerability
- Given there are many effective therapies with similar disease outcomes, there is a need for novel patient-focused endpoints to clarify treatment choice and supplement traditional endpoints like PFS in CLL trials
- Regulators such as FDA, EMA, and HTAs emphasize PRO use in oncology clinical trials, highlighting the importance of disease-specific symptom assessment and continued PRO collection to understand patient trajectories
- The proposed concept of symptom-based PFS (s-PFS) as a composite meets HTA needs (G-BA/IQWiG) and strengthens the evidence supporting PFS when OS is immature

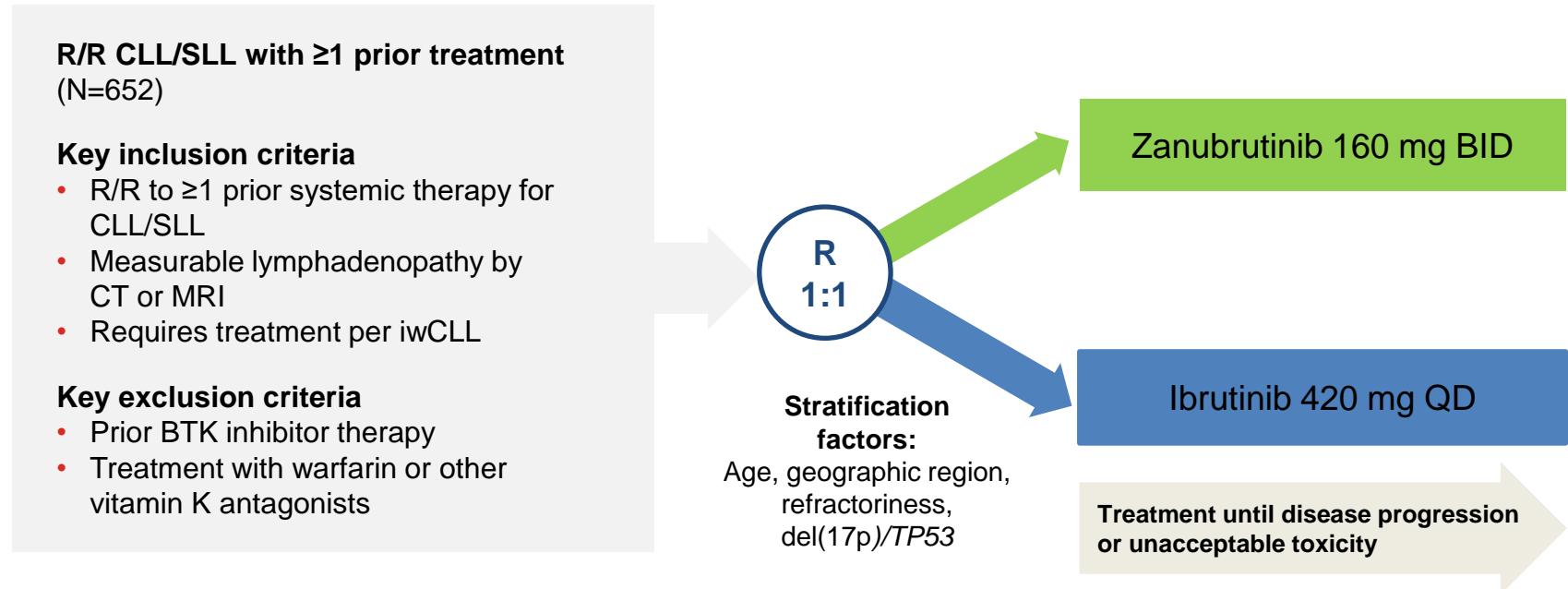
1. Brown JR, et al. *Blood*. 2024;144(26):2706-2717; 2. Tam CS, et al. *Curr Med Res Opin*. 2023;39(11):1497-1503.

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; EMA, European Medicines Agency; FDA, US Food and Drug Administration; G-BA, Gemeinsamer Bundesausschuss; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; HTA, health technology assessment agency; PFS, progression-free survival; PRO, patient-reported outcome; SLL, small lymphocytic lymphoma, s-PFS, symptom-based PFS.



American Society of Hematology

ALPINE Study Schema



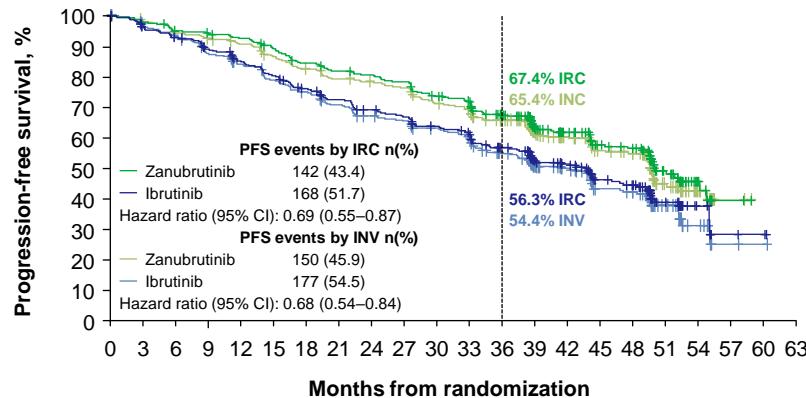
BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CT, computed tomography; MRI, magnetic resonance imaging; QD, once daily; R, randomization; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.



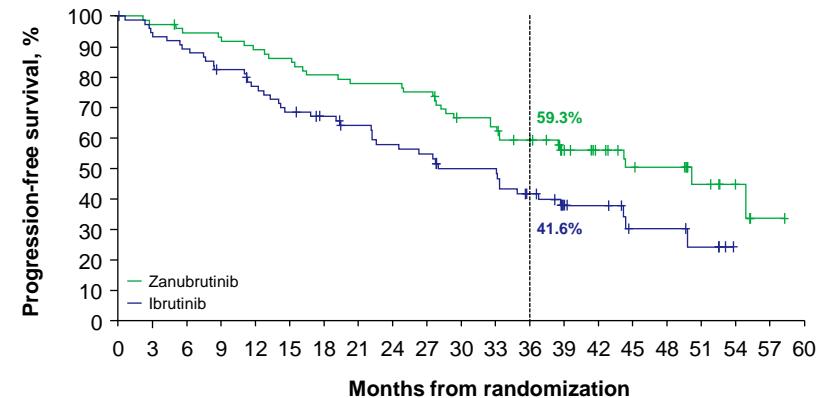
American Society of Hematology

ALPINE PFS With 3.5 Years of Follow-Up

PFS by INV and IRC (ITT)



PFS by IRC (del(17p)/TP53 mut)



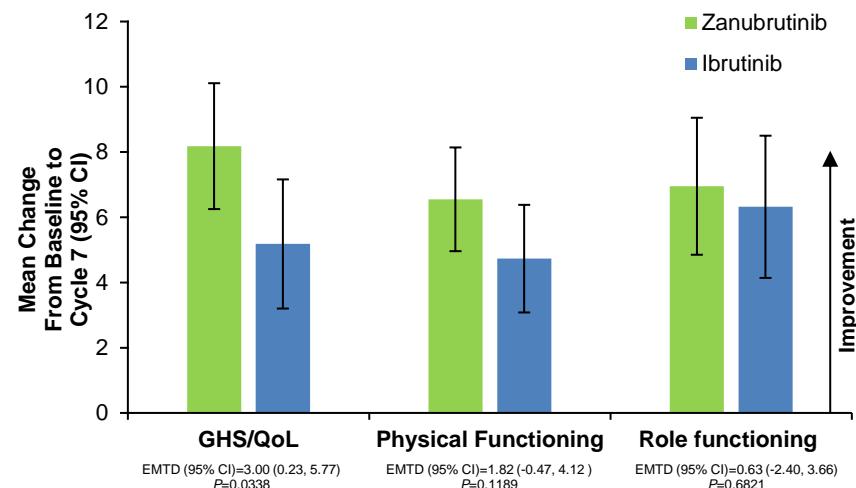
Improved PFS in patients with R/R CLL treated with zanubrutinib versus ibrutinib^{1,2}

1. Brown JR, et al. *Blood*. 2024;144(26):2706-2717; 2. Brown JR, et al. Poster presented at: 18th International Conference on Malignant Lymphoma; June, 2025; Lugano, Switzerland. CI, confidence interval; CLL, chronic lymphocytic leukemia; INV, investigator assessment; IRC, independent review committee assessment; ITT, intent to treat; mut, mutation; PFS, progression-free survival; R/R, relapsed/refractory.

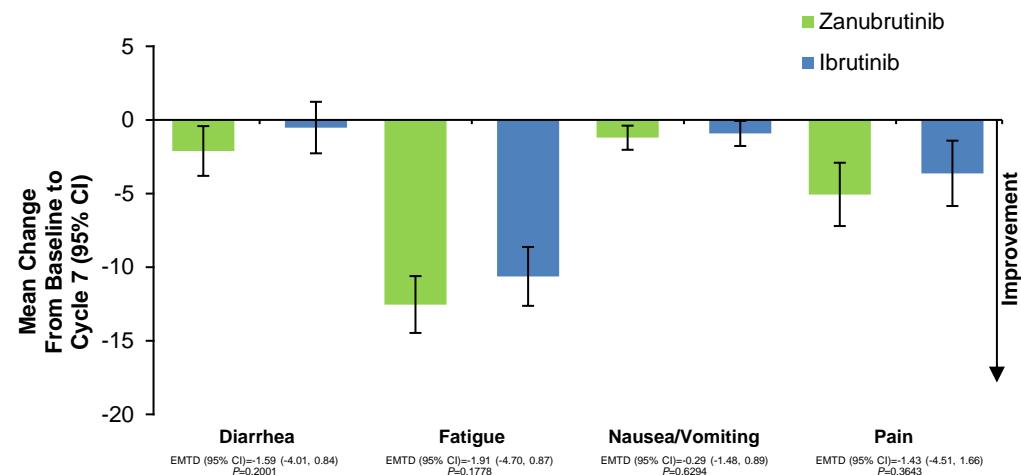


ALPINE PRO Outcomes

EORTC QLQ-C30 Mean change from baseline in GHS/QoL and functioning scales at cycle 7 (6 months) by treatment



EORTC QLQ-C30 Mean change from baseline in symptom scales at cycle 7 (6 months) by treatment



CI, confidence interval; EMTD, estimated mean treatment difference; GHS, global health status; PRO, patient-reported outcome.



Study Objectives

To examine the association between longitudinal disease-specific symptom deterioration and time to disease progression (defined as PFS events)

To identify the most relevant disease symptoms measured by PROs that are predictive of disease progression

To assess differences in symptom deterioration risk between zanubrutinib and ibrutinib

PFS, progression-free survival; PRO, patient-reported outcome.



American Society of Hematology

Methods

- **Population:** All enrolled patients with baseline and ≥ 1 evaluable post-baseline PRO (zanubrutinib vs ibrutinib; n=608)
- **PRO instrument:** EORTC-QLQ-C30
- **CLL-related symptom domains:** Fatigue, nausea/vomiting, insomnia, pain
- **Symptom scales:** Higher scores suggest worsening HRQoL
- **Definition of deterioration:** ≥ 10 -point worsening from baseline¹
- **Median number of post-baseline measurements:** 13 (range:1-21)
- **Compliance rates:** Rates were high (**>87%**) in both treatment groups at each assessment timepoint
- **All observed post-baseline PRO measurements were included**

¹PRO endpoints are selected from the most relevant disease- and treatment-related symptoms and functioning domains. 1. Osoba D, et al. *J Clin Oncol*. 1998;16(1):139-144. EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer core quality of life questionnaire; GHS, global health status; HRQoL, health-related quality of life; ITT, intent to treat; PRO, patient-reported outcome; QoL, quality of life.



Patient Characteristics

Baseline characteristics for the current analysis were balanced in both arms

Characteristic		Zanubrutinib (n=308)	Ibrutinib (n=300)
Age – n (%)	<64 years	123 (39.9)	116 (38.7)
	≥65 and <75 years	117 (38.0)	121 (40.3)
	≥75 years	68 (22.1)	63 (21.0)
	Median (min-max)	67 (35-90)	68 (35-89)
Sex – n (%)	Male	201 (65.3)	213 (71.0)
	Female	107 (34.7)	87 (29.0)
Race – n (%)	White	247 (80.2)	243 (81.0)
	Asian	45 (14.6)	42 (14.0)
	Not reported	6 (1.9)	12 (4.0)
	Other	2 (0.6)	2 (0.7)
	Black or African American	4 (1.3)	1 (0.3)
	Native Hawaiian or Other Pacific Islander	3 (1.0)	0
	Unknown	1 (0.3)	0
ECOG PS – n (%)	2	6 (1.9)	9 (3.0)
	1	181 (58.8)	177 (59.0)
	0	121 (39.3)	114 (38.0)
Region – n (%)	Asia	47 (15.3)	43 (14.3)
	Australia/New Zealand	27 (8.8)	28 (9.3)
	Europe	184 (59.7)	177 (59.0)
	USA	50 (16.2)	52 (17.3)
Del(17p) status – n (%)	Absent	239 (77.6)	235 (78.3)
	Present	69 (22.4)	65 (21.7)
Refractory status – n (%)	No	224 (72.7)	216 (72.0)
	Yes	84 (27.3)	84 (28.0)

ECOG PS, Eastern Cooperative Oncology Group performance status; min-max, minimum-maximum.



American Society of Hematology

Analytical Framework

Mixed-effects logistic regression



To estimate the odds of symptom worsening for each patient

Cox proportional hazards model



To model time to investigator-assessed PFS

A joint model framework



To estimate prognostic association between the PRO-symptom worsening and time to PFS



The coefficient indicates the change in the HR of progression per prespecified PRO change (e.g., per 10-point deterioration)

Coefficient interpretation: $HR > 1$ = symptom worsening predicts risk of earlier disease progression

Stratification factors: Age (<65/≥65), region (China/non-China), refractory status, *del(17p)*/*TP53* mutation status

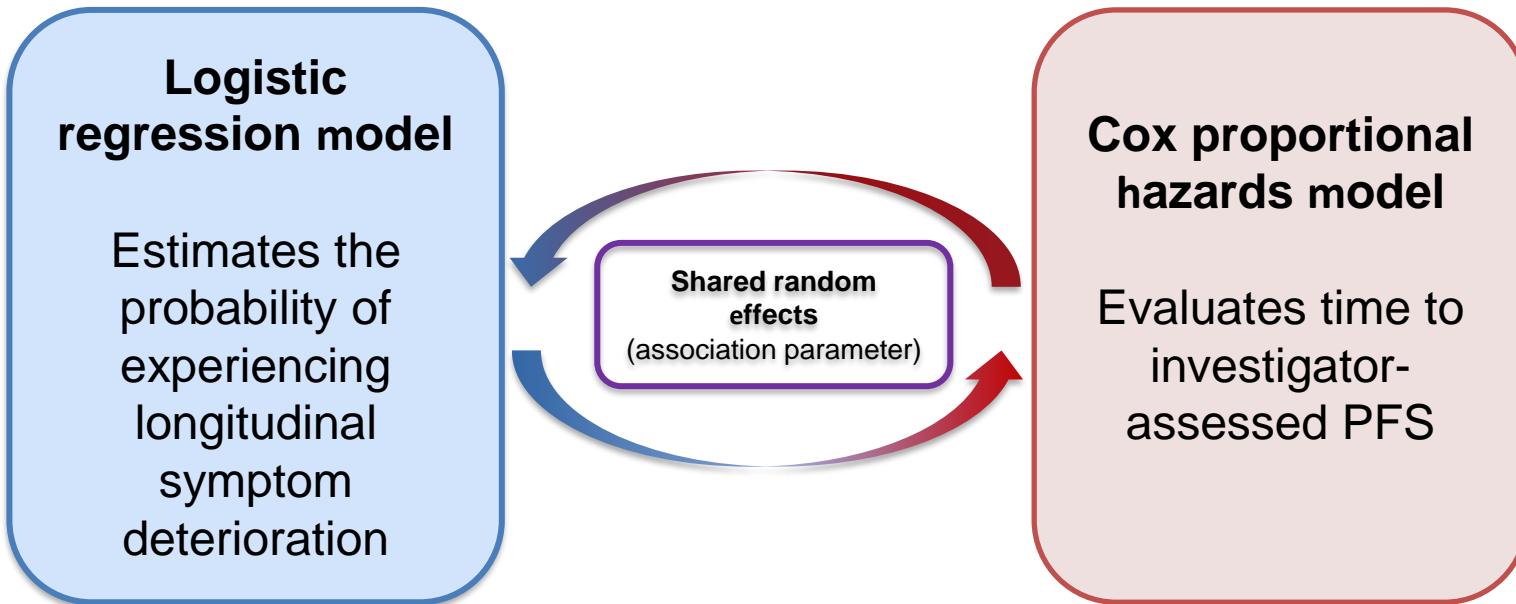
Software: JMbayes2 in R (v4.3.2)

HR, hazard ratio; PFS, progression-free survival; PRO, patient-reported outcome.



American Society of Hematology

Joint Model Framework



Association coefficient interpretation:

HR>1 indicates increase hazard of disease progression when a PRO worsening event is observed

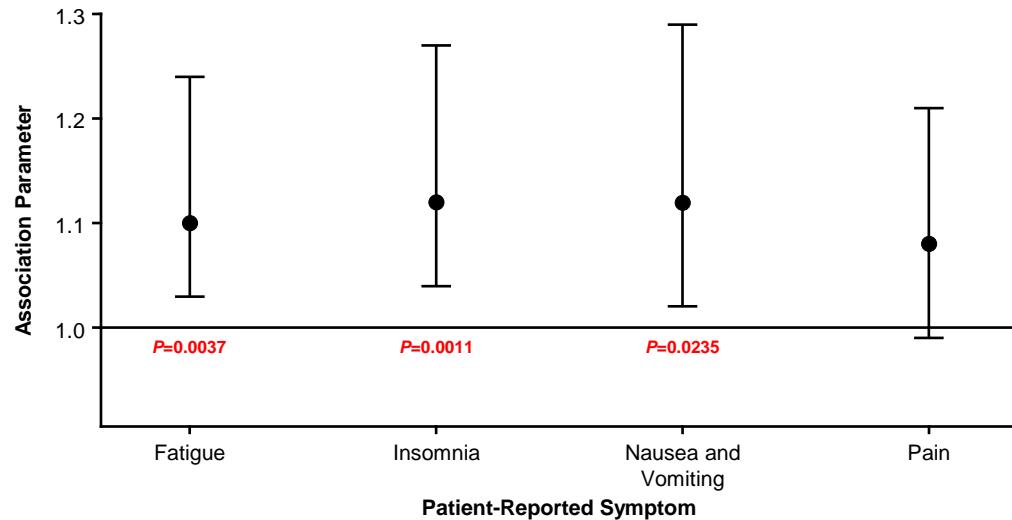
HR, hazard ratio; PFS, progression-free survival.



American Society of Hematology

Long-Term Patient-Reported Symptoms Were Significantly Associated With Increased Risk of Disease Progression

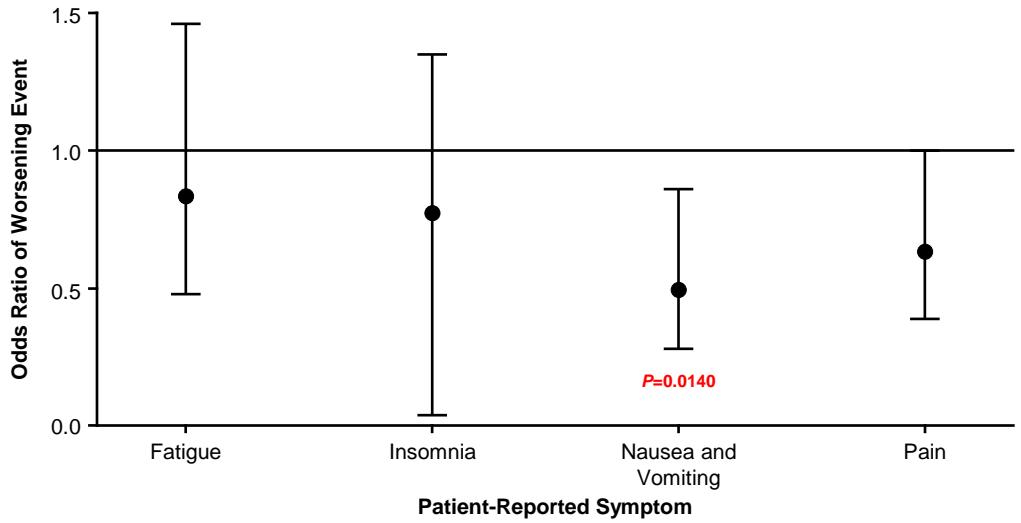
- Deterioration in patient-reported **fatigue, insomnia, and nausea/vomiting** was significantly associated with increased risk of disease progression



Parameter	Association Parameters and 95% Confidence Intervals			
	Fatigue	Insomnia	Nausea and Vomiting	Pain
Association Parameter	1.10 (1.03, 1.24)	1.12 (1.04, 1.27)	1.12 (1.02, 1.29)	1.08 (0.99, 1.21)

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

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



Parameter	Odds Ratios and 95% Confidence Intervals			
	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)

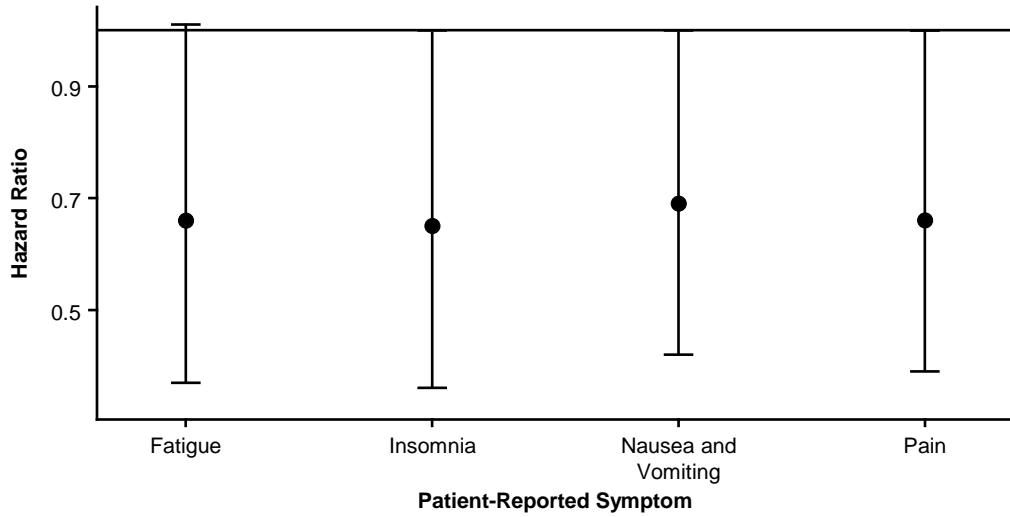
Odds ratios <1 indicate that zanubrutinib is protective relative to ibrutinib.



American Society of Hematology

Zanubrutinib Improved PFS vs Ibrutinib Across Disease Symptom Domains

- Risk of disease progression or death was **~30% lower** with zanubrutinib compared with ibrutinib when assessed by PRO symptom domains



Parameter	Hazard Ratios and 95% Confidence Intervals			
	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)

HRs <1 indicate that zanubrutinib is protective relative to ibrutinib
HR, hazard ratio; PFS, progression-free survival.



American Society of Hematology

Conclusions

- These findings support the association between worsening of clinically relevant patient-reported symptoms and disease progression
- Deterioration and increase in patient-reported fatigue, insomnia, and nausea/vomiting emerged as strong symptomatic indicators of disease progression
- Additionally, patients on zanubrutinib showed reduced risk of deterioration of symptoms associated with earlier disease progression
- These results underscore the potential for defining and developing PRO symptoms and s-PFS as a composite endpoint for analysis in future CLL trials
- In future CLL studies, s-PFS could be examined as a potential endpoint to showcase the treatment effectiveness

Thank you!

Q&A



American Society of Hematology