Patient-Reported Outcome (PRO)-Based Recurrent Symptomatic Deterioration Predicts Disease Progression: Results From the ALPINE Trial

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INTRODUCTION

- PRO-based symptom endpoints are rarely associated with treatment efficacy in oncology trials, including those conducted in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
- Time-to-deterioration analyses of key PRO symptoms (eg, fatigue) and functioning (eg, physical function) are routinely employed in oncology clinical trials to evaluate the effects of treatment on a single deterioration event
  - However, PRO-based deterioration frequently has "transient" event times; for example, a patient may experience multiple fatigue deteriorations over time
  - Therefore, transient event times are best modeled as recurrent events
  - Under a recurrent event process, the time to each unique deterioration is modeled, and the overall risk of recurrent deterioration is estimated within a survival model accounting for the correlation among recurrent deterioration events
- The objective of the current analyses was to develop a joint model to examine the association between time to recurrent PRO-based deterioration and disease progression (defined as PFS events) in patients enrolled in the ALPINE trial

METHODS

Study Design and Patients

- These analyses were conducted using data from the ALPINE trial
  - ALPINE (BGB-3111-305; NCT03734016), a phase 3, randomized, open-label, multinational trial of adult patients with relapsed or refractory CLL/SLL, was performed to compare the efficacy and safety of zanubrutinib with ibrutinib monotherapy[1]
  - Patients were randomized 1:1 to receive zanubrutinib 160 mg orally twice daily or ibrutinib 420 mg orally once daily until disease progression or patient withdrawal
  - The study was carried out in accordance with Good Clinical Practice Guidelines, the principles of the Declaration of Helsinki, and local laws and regulations

Measures

- PRO-based symptoms were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30), which is designed to assess the overall health-related quality of life of patients with cancer during the past week[2]
  - Six QLQ-C30 symptom scales were analyzed: appetite, diarrhea, dyspnea, fatigue, nausea/vomiting, and pain. The QLQ-C30 was administered at baseline and cycle 1 and then every third cycle until the end of treatment; each cycle constituted 28 days
- Investigator-assessed PFS was analyzed as the terminal event measure
- Deterioration threshold was defined using Osoba's Criterion[3] (ie, any postbaseline change of ≥10)
  - Unique recurrent symptomatic deterioration (RS-D) events from cycles 4 to 43 were identified using this threshold
  - Two deterioration events had to be separated by non-events to qualify as a unique RS-D event

Statistical Analyses

- All randomized patients in the ITT population who completed the baseline and ≥1 post-baseline QLQ-C30 assessment were eligible
  - The analytic cohort was based on the ITT population with both PFS and RS-D event data
- Treatment efficacy for the symptoms was evaluated using a three-component joint survival model (treatment effect was coded as zanubrutinib vs ibrutinib with ibrutinib as the reference group) that linked the following components:
  - A linear mixed model for change from baseline (CFBL) in symptom scores to assess the association between change in symptom scores and RS-D events and disease progression
  - A Frailty Cox proportional hazards model for time to RS-D events
  - A Cox proportional hazards model for PFS (terminal event) to evaluate the RS-D event frailty prediction of PFS
- The joint model provides a comprehensive adjustment for missing data bias
  - The linear mixed model directly adjusts for data missing at random
  - The terminal event survival models adjust the linear mixed model for data missing not at random
- All models were adjusted by the following stratification factors: age (<65 years vs ≥65 years), geographic region (China vs non-China), refractory status (yes vs no), del(17p)/TP53 mutation status (present vs absent), and cancer type (CLL vs SLL)
- Analyses were conducted using the JMBayes2 package in R (version 4.3.2)
  - Model and parameter convergence were evaluated using trace and density plots and the $\hat{R}$ statistic

RESULTS

- At data cutoff (September 15, 2023), the ITT population consisted of a total of 652 patients (327 received zanubrutinib and 325 received ibrutinib)
  - Patient demographics and baseline disease characteristics were generally balanced across the arms
- Fifty patients were excluded from the current analyses because they did not have any PRO data; a total of 601 patients (zanubrutinib, n=308 [51.2%]; ibrutinib, n=293 [48.8%]) were included in the PFS joint models
- Using the QLQ-C30 fatigue domain as an example, the number of recurrent symptomatic deterioration events ranged from 0 to 6 (**Table 1**)

Table 1. Number of Recurrent Fatigue Symptom Deterioration Events

Number of Recurrent Events	n (%)	Cumulative n (%)
0	149 (24.8)	149 (24.8)
1	249 (41.4)	398 (66.1)
2	95 (15.8)	493 (81.9)
3	65 (10.8)	558 (92.7)
4	33 (5.5)	591 (98.2)
5	10 (1.7)	601 (99.8)
6	1 (0.2)	602 (100)

- In the linear mixed model, treatment efficacy for zanubrutinib compared with ibrutinib was observed for diarrhea (-2.62 [95% CI, -4.49 to -0.67]; *P*=0.0089) and nausea/vomiting (-0.88 [95% CI, -1.65 to -0.10]; *P*=0.0251) (**Table 2**)

Table 2. Zanubrutinib vs Ibrutinib Efficacy From Cycles 4 to 43 for Recurrent Symptomatic Deterioration Events in Three-Component Joint Model

Terminal Event	QLQ-C30 DOMAIN	Effect	β (95% CI)	*P*	CNVG
Progression-free survival	Appetite	Zanubrutinib	-1.88 (-3.88 to 0.13)	0.0669	1.0014
		Time	0.02 (-0.03 to 0.08)	0.4156	1.0144
		Zanubrutinib x time	-0.01 (-0.08 to 0.06)	0.7253	1.0091
	Diarrhea	Zanubrutinib	-2.62 (-4.49 to -0.67)	0.0089	1.0101
		Time	-0.04 (-0.09 to 0.02)	0.1796	1.0331
		Zanubrutinib x time	0.04 (-0.03 to 0.11)	0.2727	1.0078
	Dyspnea	Zanubrutinib	-0.47 (-2.52 to 1.66)	0.6502	1.0093
		Time	0.03 (-0.03 to 0.09)	0.3382	1.0259
		Zanubrutinib x time	0.00 (-0.09 to 0.08)	0.9391	1.0222
	Fatigue	Zanubrutinib	-0.54 (-2.80 to 1.78)	0.6584	1.0052
		Time	0.00 (-0.06 to 0.06)	0.9453	1.0055
		Zanubrutinib x time	0.03 (-0.05 to 0.11)	0.4491	1.0210
	Nausea/ vomiting	Zanubrutinib	-0.88 (-1.65 to -0.10)	0.0251	1.0089
		Time	-0.02 (-0.05 to 0.00)	0.0913	1.0203
		Zanubrutinib x time	0.04 (0.01 to 0.08)	0.0156	1.0129
	Pain	Zanubrutinib	-1.29 (-3.50 to 1.02)	0.2656	1.0058
		Time	-0.04 (-0.10 to 0.03)	0.2442	1.0135
		Zanubrutinib x time	0.06 (-0.02 to 0.14)	0.1418	1.0181

CNVG represents convergence of parameter, based on $\hat{R}$ statistic (values of 1 indicate perfect convergence). All estimates achieved acceptable convergence. Time in this analysis is months since baseline. Significant effects are highlighted in blue. Models were adjusted for the following: region, del(17p) mutation, age >65 years, refractory status, cancer type (CLL/SLL), and baseline COA score; efficacy reference drug is ibrutinib.
CLL, chronic lymphocytic leukemia; COA, clinical outcome assessment; QLQ-C30, Quality of Life Questionnaire Core-30; SLL, small lymphocytic lymphoma.

- In the recurrent event models for symptomatic deterioration, after adjusting for PFS, CFBL in corresponding symptoms, and stratification factors, there was no difference between treatment arms in risk of RS-D events (**Table 3**)
  - As expected, increasing CFBL in all symptoms (appetite, diarrhea, dyspnea, fatigue, nausea/vomiting, pain) was associated with increased risk of RS-D events, irrespective of treatment (**Table 3**). This is reflected in the linear predictor coefficient (eg, for appetite: Lin Pred = AP CFBL: R-AP-DET)
- In the PFS model, after adjusting for recurrent symptomatic deterioration, CFBL in corresponding symptoms, and stratification factors, zanubrutinib treatment was associated with statistically significant reduction in the risk of investigator-assessed PFS events when compared with ibrutinib (**Table 3**; PFS HRs after adjusting for symptoms of appetite: 0.55, *P*=0.0093; diarrhea: 0.60, *P*=0.0202; dyspnea: 0.59, *P*=0.0189; fatigue: 0.71, *P*=0.0191; nausea/vomiting: 0.66, *P*=0.0087; pain: 0.69, *P*=0.0144)
- Increasing RS-D events for appetite, diarrhea, and dyspnea were strongly associated with risk of PFS, irrespective of treatment (**Table 3**)
- Convergence for the dyspnea frailty prediction exhibited incomplete convergence ($\hat{R}$=1.82)

Table 3. Zanubrutinib vs Ibrutinib Efficacy in Three-Component Joint Model

Terminal Event	QLQ-C30 DOMAIN	Effect	HR (95% CI)	*P*	CNVG
Progression-free survival	Appetite	Zanubrutinib: R-AP-DET	0.95 (0.58-1.50)	0.8276	1.0020
		Zanubrutinib: PFS	0.55 (0.30-0.90)	0.0093	1.0376
		Lin Pred = AP CFBL: R-AP-DET	1.14 (1.12-1.16)	0.0000	1.0040
		Lin Pred = AP CFBL: PFS	0.99 (0.97-1.00)	0.0151	1.0213
		R-AP Det frailty: PFS	4.55 (2.25-6.87)[a]	0.0000	1.1340
	Diarrhea	Zanubrutinib: R-DI-DET	1.03 (0.64-1.64)	0.9009	1.0117
		Zanubrutinib: PFS	0.60 (0.34-0.94)	0.0202	1.0271
		Lin Pred = DI CFBL: R-DI-DET	1.16 (1.13-1.19)	0.0000	1.1180
		Lin Pred = DI CFBL: PFS	1.00 (0.98-1.01)	0.9242	1.0067
		R-DI Det frailty: PFS	3.47 (1.61-5.92)[a]	0.0000	1.0681
	Dyspnea	Zanubrutinib: R-DY-DET	1.02 (0.65-1.58)	0.9164	1.0093
		Zanubrutinib: PFS	0.59 (0.29-0.92)	0.0189	1.1236
		Lin Pred = DY CFBL: R-DY-DET	1.13 (1.11-1.15)	0.0000	1.0125
		Lin Pred = DY CFBL: PFS	0.99 (0.98-1.00)	0.1720	1.1156
		R-DY Det frailty: PFS	3.73 (1.58-6.51)[a]	0.0000	1.8209
	Fatigue	Zanubrutinib: R-FA-DET	0.98 (0.70-1.35)	0.9124	1.0095
		Zanubrutinib: PFS	0.71 (0.51-0.95)	0.0191	1.0459
		Lin Pred = FA CFBL: R-FA-DET	1.10 (1.09-1.11)	0.0000	1.0835
		Lin Pred = FA CFBL: PFS	1.01 (1.00-1.01)	0.1556	1.0296
		R-FA Det frailty: PFS	1.74 (-3.00 to 5.83)[a]	0.3847	1.7081
	Nausea/ vomiting	Zanubrutinib: R-NV-DET	0.92 (0.58-1.44)	0.7340	1.0238
		Zanubrutinib: PFS	0.66 (0.37-0.92)	0.0087	1.3159
		Lin Pred = NV CFBL: R-NV-DET	1.28 (1.23-1.32)	0.0000	1.0643
		Lin Pred = NV CFBL: PFS	1.01 (0.98-1.03)	0.6064	1.0843
		R-NV Det frailty: PFS	2.63 (-2.81 to 6.94)[a]	0.3387	2.0101
	Pain	Zanubrutinib: R-PA-DET	0.87 (0.64-1.16)	0.3904	1.0072
		Zanubrutinib: PFS	0.69 (0.48-0.93)	0.0144	1.0101
		Lin Pred = PA CFBL: R-PA-DET	1.09 (1.08-1.10)	0.0000	1.0566
		Lin Pred = PA CFBL: PFS	1.00 (0.99-1.01)	0.5400	1.0086
		R-PA Det frailty: PFS	2.32 (-0.31 to 4.77)[a]	0.0700	1.0210

CNVG represents convergence of parameter, based on $\hat{R}$ statistic (values of 1 indicate perfect convergence). All estimates achieved acceptable convergence. Time in this analysis is months since baseline. Significant effects are highlighted blue. Models were adjusted for the following: region, del(17p) mutation, age >65 years, refractory status, cancer type (CLL/SLL), and baseline COA score; efficacy reference drug is ibrutinib.
[a]Association parameter and not HR.
CLL, chronic lymphocytic leukemia; COA, clinical outcome assessment; R-AP-DET, recurrent appetite deterioration; R-DI-DET, recurrent diarrhea deterioration; R-DY-DET, recurrent dyspnea deterioration; R-FA-DET, recurrent fatigue deterioration; R-NV-DET, recurrent nausea/vomiting deterioration; R-PA-DET, recurrent pain deterioration; SLL, small lymphocytic lymphoma.

CONCLUSIONS

- After predicting PFS from the risk of recurrent symptomatic deterioration events and using a joint model to adjust for baseline stratification factors and change from baseline in corresponding symptoms, zanubrutinib remained superior to ibrutinib with respect to disease progression in the ALPINE trial
- Recurrent symptomatic deterioration in appetite, diarrhea, and dyspnea were leading predictors for risk of disease progression
- These analyses suggest that patient reporting of deterioration in these symptoms may indicate a need for increased clinical monitoring

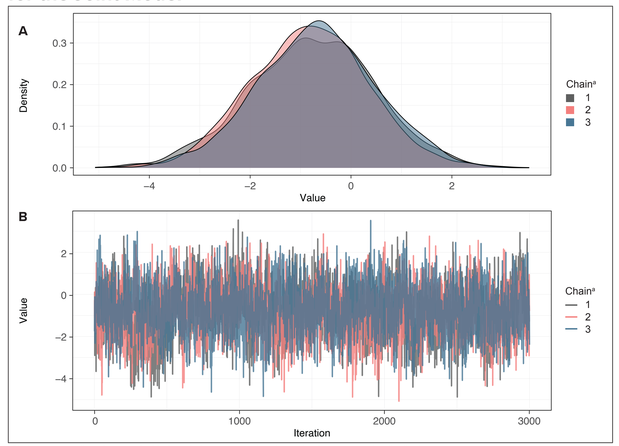
DISCUSSION

- The three-component joint model detected zanubrutinib efficacy in diarrhea and nausea while simultaneously preserving zanubrutinib efficacy in PFS and demonstrating the relationship between clinical progression and recurrent deterioration in appetite, diarrhea, and dyspnea
- These preliminary analyses provide a mechanism for modeling PRO data in clinical trials that may help illuminate additional patient-centric therapeutic benefits
  - To our knowledge, this method has not previously been used for PROs in the oncology therapeutic domain

Joint Model

- Patients were censored if they experienced no recurrent events or disease progression by end of study
- Convergence plots for the joint model indicated satisfactory convergence of the Bayesian integral-based marginalization (**Figure 1A and 1B**)

Figure 1. Convergence Density (A) and Convergence Trace (B) for the Joint Model



[a]Chains are sampling elements for Markov chains, autocorrelated samples from a posterior distribution.

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DISCLOSURES
Jennifer Brown has served as a consultant for AbbVie, Acerta/AstraZeneca, Alloplex Biotherapeutics, BeiGene, Bristol Myers Squibb/Juno/Celgene, Catapult, Genentech/Roche, Grifols Worldwide Operations, Hutchmed, iOnctura, Janssen, Kite, Loxo/Lilly, MEI Pharma, Merck Sharp & Dohme, Numab Therapeutics, Pfizer, and Pharmacyclics; and has received research funding from BeiGene, Gilead, iOnctura, Loxo/Lilly, MEI Pharma, Verastem/SecuraBio, and TG Therapeutics.

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