Abstract: P1834

Title: PATIENT-REPORTED OUTCOME (PRO)–BASED RECURRENT SYMPTOMATIC DETERIORATION PREDICTS DISEASE PROGRESSION: RESULTS FROM THE ALPINE TRIAL

Abstract Type: e-Poster Presentation

Topic: Chronic lymphocytic leukemia and related disorders - Clinical

Background:

Time to deterioration or time until definite deterioration analyses of key PRO symptoms (eg, fatigue) and functioning (eg, physical function) are routinely employed in oncology trials to evaluate the effects of treatment on a single deterioration event. However, PRO-based deterioration has “transient” event times: a patient may experience multiple fatigue deteriorations over time. Transient event times are best modeled as recurrent events. This study focuses on fatigue deterioration given that anemia-mediated fatigue is common in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and examines the association between recurrent PRO-based deterioration and progression-free survival (PFS).

Aims:

This study examines the association between time to recurrent PRO-based deterioration and disease progression.

Methods:

The ALPINE trial (BGB-3111-305; NCT03734016) was a multinational, open-label, randomized, phase 3 study of adult patients with relapsed or refractory (R/R) CLL/SLL to compare the efficacy and safety of zanubrutinib versus ibrutinib monotherapy (Brown et al. *NEJM.* 2023). Anchor-based meaningful within-patient change thresholds defining EORTC-QLQ-C30 (C30) fatigue deterioration were computed using median change from baseline (CFBL) to cycle 13 data anchored on the C30 global health scale. Unique recurrent fatigue deterioration (RFA-D) events from cycles 4 to 43 were identified using the threshold. PFS and RFA-D events were modeled via Cox and Cox frailty proportional hazards, respectively, within a joint survival model (JM). The RFA-D event frailty prediction of PFS was used to evaluate the relationship between RFA-D events and PFS. The JM included a linear mixed model for CFBL in C30 pain scores to adjust for changes in pain and assess the association between change in pain and RFA-D events and progression. All 3 models were adjusted for geographic region, age, del(17p)/*TP53* mutation status, refractory status, and cancer type (CLL vs. SLL). All analyses were conducted using the JMBayes2 package in R version 4.3.2, applying to the ITT population with both PFS and RFA-D event data.

Results:

Of the 602 patients, 149 (24.8%) experienced zero RFA-D events; and 249 (41.4%), 95 (15.8%), 65 (10.8%), 33 (5.5%), 10 (1.7%), and one (0.2%) experienced one, two, three, four, five, or six RFA-D events, respectively. Patients were censored if they experienced no recurrent events or no progression by study end. In the PFS model, after adjusting for stratification factors and CFBL in pain and prediction by risk of RFA-D events, zanubrutinib was associated with a 31% reduction in the risk of investigator-assessed progression events (hazard ratio [HR]=0.69; *P*=0.0193) when compared with ibrutinib (Table). Increasing RFA-D events were positively associated with increased risk of progression (association parameter, 3.46; *P*=0.0467), irrespective of treatment. In the recurrent event model for fatigue deterioration, there was no difference between arms in risk of RFA-D events (*P*=0.7120). Increasing pain deterioration was associated with increased risk of RFA-D events, irrespective of treatment (*P*=0.0024).

Summary/Conclusion:

After predicting PFS from the risk of RFA-D events and adjusting for baseline stratification factors and CFBL in pain, zanubrutinib remained more protective than ibrutinib against progression. Recurrent fatigue deterioration predicted the risk of disease progression before disease progression confirmation by the investigator. Analyses of other disease-related PRO endpoints in the ALPINE trial are being completed and will be reported.

Table. JM survival submodel estimates

Event	Effect	HR (95% CI)	*P* value
Progression	Zanubrutinib	0.69 (0.50–0.94)	0.0193
Progression	Region Asia	1.04 (0.68–1.58)	0.8260
Progression	Del(17p) present	1.66 (1.19–2.39)	0.0044
Progression	Older than 65 years	1.32 (0.96–1.80)	0.0920
Progression	Not refractory	0.76 (0.55–1.04)	0.0971
Progression	CLL	0.66 (0.29–1.83)	0.3207
Progression	C30 Pain	1.00 (1.00–1.01)	0.3940
Progression	RFA-D frailty	3.46 (0.07–6.38)[a]	0.0467
RFA-D	Zanubrutinib	0.94 (0.69–1.25)	0.7120
RFA-D	Region Asia	0.98 (0.71–1.33)	0.8940
RFA-D	Del(17p) present	0.84 (0.66–1.06)	0.1482
RFA-D	Older than 65 years	1.22 (1.01–1.47)	0.0331
RFA-D	Not refractory	0.96 (0.79–1.17)	0.6949
RFA-D	CLL	0.67 (0.46–1.04)	0.0813
RFA-D	C30 Pain	1.01 (1.00–1.01)	0.0024

[a]Association parameter and not HR.

Keywords: Progression, Survival prediction, Quality of life, Patient reported outcomes