

Associations Between Patient-Reported Outcomes and Progression-Free Survival in Patients With Extensive-Stage Small Cell Lung Cancer: Results From the RATIONALE-312 Trial

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CONCLUSIONS

- Patients receiving tislelizumab + chemotherapy had reduced patient-reported chest pain, and the PFS benefit remained robust even after adjusting for stratification factors and longitudinal PRO symptom trajectories
- Recurrent symptomatic deterioration in physical functioning was associated with increased hazard of progression events (disease progression/death), further demonstrating the relationship between clinical progression and recurrent PRO-based symptom deterioration
- Tislelizumab + chemotherapy was associated with a statistically significant reduced risk of progression events (disease progression/death) for QLQ-C30 and QLQ-LC13 domains compared to placebo + chemotherapy
- Findings from this study suggest that PFS is associated with PROs, highlighting the potential benefit of considering both PFS and patient-reported symptoms/HRQoL when evaluating treatment benefits
- Overall, these results, together with previously reported clinical efficacy and safety data, reinforce the use of tislelizumab + chemotherapy as a first-line treatment option for patients with ES-SCLC

INTRODUCTION

- Extensive-stage small cell lung cancer (ES-SCLC) is an aggressive subtype of lung cancer with limited treatment options and poor outcomes^{1,2}
- Patients with ES-SCLC often experience high symptom burden and declines in health-related quality of life (HRQoL)³
- In the phase 3 RATIONALE-312 trial (NCT04005716), first-line tislelizumab + chemotherapy significantly improved overall survival (OS) (hazard ratio [HR]: 0.75 [95% confidence interval (CI): 0.61-0.93]; $P=0.0040$) and progression-free survival (PFS) (HR: 0.64 [95% CI: 0.52-0.78]; $P<0.0001$) and maintained or improved patient-reported outcomes (PROs) versus placebo + chemotherapy^{4,5}
- Although adding tislelizumab to chemotherapy improves outcomes, there is limited evidence evaluating the associations between PFS and symptoms/HRQoL in ES-SCLC—an important gap given the growing emphasis on patient experience and German Institute for Quality and Efficiency in Health Care requirement to consider mortality/morbidity alongside patient-reported symptoms in benefit-risk evaluations^{6,9}
- To address this gap, the objective of the current post hoc analysis was to empirically evaluate the association between PFS and patient-reported symptoms among patients with ES-SCLC enrolled in the RATIONALE-312 trial

METHODS

Study Design and Patients

- These analyses were conducted using RATIONALE-312 trial data
- RATIONALE-312 (NCT04379635) was a randomized, double-blind, placebo-controlled, multicenter, phase 3 trial conducted at 51 centers in the People's Republic of China
- Eligible adult patients in China with previously untreated ES-SCLC were randomly assigned (1:1) to receive four cycles of intravenous tislelizumab 200 mg or placebo, in combination with etoposide and a platinum agent (cisplatin or carboplatin) as induction treatment, followed by tislelizumab 200 mg or placebo as maintenance

Measures

- PRO-based symptom deterioration endpoints were assessed using the core European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30) and the EORTC Lung Cancer-specific Module (QLQ-LC13)
- Investigator-assessed PFS was analyzed as the clinical event
- PRO-based recurrent symptom deterioration scores were defined using Osoba's threshold of clinically meaningful change ≥ 10 points⁸
- Two deterioration events had to be separated by non-events to qualify as a unique recurrent symptom deterioration event

Statistical Analyses

- All randomized patients in the intent-to-treat (ITT) population who completed the baseline and ≥ 1 postbaseline QLQ-C30 and QLQ-LC13 assessment were eligible
- The analytic cohort was based on the ITT population with both PFS and recurrent symptom deterioration event data
- Treatment efficacy for PRO-based symptom endpoints were analyzed using joint survival models (treatment effect was coded as tislelizumab vs placebo with tislelizumab as the effect group) that linked the following three components:
 - A linear mixed model (LMM) for change from baseline in PRO scores with treatment effect, study month effect, treatment by study month interaction, and stratification factor covariates
 - A recurrent events frailty Cox model for PRO-based recurrent symptom deterioration events
 - A Cox proportional hazards model with treatment and stratification factor covariate for PFS
 - The threshold for statistical significance was established at $P<0.05$
- All models were adjusted for the following randomization factors: ECOG performance status (0 vs 1), brain metastasis, and investigator-chosen chemotherapy (cisplatin vs carboplatin)
- All analyses were conducted using R (4.3.2) and the JMbayes2 (0.4-5), nlme (3.1-164), and survival (3.5-7) packages

RESULTS

- At the data cutoff of April 19, 2023, the ITT population consisted of a total of 457 patients randomized to receive tislelizumab (n=227) or placebo (n=230)
- The joint model analytic sample in this study included a total of 433 patients (tislelizumab, n=216; placebo, n=217)
- Twenty-four patients were omitted due to incomplete or missing PRO data

Linear Mixed Effects Submodel Results: Tislelizumab Efficacy for Change From Baseline in PRO Scores

- In the LMM, compared with placebo + chemotherapy, tislelizumab + chemotherapy was associated with a significant improvement in QLQ-LC13 chest pain scores (-2.597 [95% CI: -4.70, -0.47]; $P=0.0158$) (Table 1)

Table 1. Joint Model-Adjusted Linear Mixed Model for Change From Baseline in QLQ-C30 and QLQ-LC13 Domains

EORTC Domain	Parameter	β (95% CI)	P	\hat{R}^2
QLQ-C30 GHS/QoL	PRO Δ_{BL} -T+C treatment effect ^b	1.197 (-1.499, 3.872)	0.377	1.00
	PRO Δ_{BL} -T+C treatment ^b × time ^c	0.003 (-0.319, 0.313)	0.985	1.01
QLQ-C30 physical functioning	PRO Δ_{BL} -T+C treatment effect ^b	0.473 (-1.394, 2.320)	0.617	1.01
	PRO Δ_{BL} -T+C treatment ^b × time ^c	0.194 (-0.196, 0.587)	0.336	1.02
QLQ-LC13 coughing	PRO Δ_{BL} -T+C treatment effect ^b	2.061 (-1.113, 5.209)	0.196	1.02
	PRO Δ_{BL} -T+C treatment ^b × time ^c	-0.820 (-1.605, -0.085)	0.029	1.07
QLQ-LC13 dysphagia	PRO Δ_{BL} -T+C treatment effect ^b	-0.342 (-1.739, 1.067)	0.633	1.00
	PRO Δ_{BL} -T+C treatment ^b × time ^c	0.013 (-0.149, 0.165)	0.851	1.01
QLQ-LC13 dyspnea	PRO Δ_{BL} -T+C treatment effect ^b	1.028 (-1.112, 3.176)	0.347	1.00
	PRO Δ_{BL} -T+C treatment ^b × time ^c	-0.293 (-0.553, -0.043)	0.021	1.02
QLQ-LC13 hemoptysis	PRO Δ_{BL} -T+C treatment effect ^b	-0.419 (-1.182, 0.339)	0.280	1.02
	PRO Δ_{BL} -T+C treatment ^b × time ^c	-0.002 (-0.027, 0.019)	0.822	5.21
QLQ-LC13 pain in arm or shoulder	PRO Δ_{BL} -T+C treatment effect ^b	-1.560 (-3.743, 0.625)	0.160	1.00
	PRO Δ_{BL} -T+C treatment ^b × time ^c	0.006 (-0.020, 0.031)	0.718	2.19
QLQ-LC13 chest pain	PRO Δ_{BL} -T+C treatment effect ^b	-2.597 (-4.700, -0.473)	0.016	1.01
	PRO Δ_{BL} -T+C treatment ^b × time ^c	0.323 (0.286, 0.363)	<0.001	5.92
QLQ-LC13 peripheral neuropathy	PRO Δ_{BL} -T+C treatment effect ^b	-0.337 (-2.258, 1.576)	0.721	1.00
	PRO Δ_{BL} -T+C treatment ^b × time ^c	0.125 (-0.103, 0.355)	0.291	1.02

Notes: Each model was adjusted for the following stratification factors: age (<65 years vs ≥ 65 years of age), geographic region (China vs non-China), refractory status (yes vs no), del(17p)/TP53 mutation status (present vs absent), cancer type (CLL vs SLL), and baseline PRO measurement (in the linear mixed models). Significant effects are highlighted in blue. Markov chain trace and density plots were also used to characterize quality of model convergence. An \hat{R}^2 statistic with a value of 1.2 indicated acceptable convergence. ^aTreatment effect was coded as tislelizumab versus placebo with the former as the effect group. ^bTime was defined as months since baseline. ^cAbbreviations: Δ_{BL} , change from baseline; CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; GHS/QoL, global health status/quality of life; HR, hazard ratio; PRO, patient-reported outcome; QLQ-C30, Quality of Life Questionnaire – Core 30; QLQ-LC13, Quality of Life Questionnaire – lung cancer module; T+C, tislelizumab + chemotherapy.

Survival Submodel Results: Tislelizumab Efficacy for Change From Baseline in PRO Scores

- In the recurrent event survival model (longitudinal effect), higher (better) GHS/QoL and physical functioning were significantly protective against recurrent symptomatic deterioration events (HR: 0.96 and 0.99, respectively; both $P<0.001$). Conversely, higher (worse) scores for QLQ-LC13 symptom domains predicted greater risk (HR range: 1.12-1.67; all $P<0.001$) (Table 2)
- Increasing recurrent symptomatic deterioration events for physical functioning (frailty) were significantly associated with shorter PFS (disease progression/death), regardless of treatment ($P=0.018$) (Table 2), indicating that physical functioning is prognostic for earlier PFS events

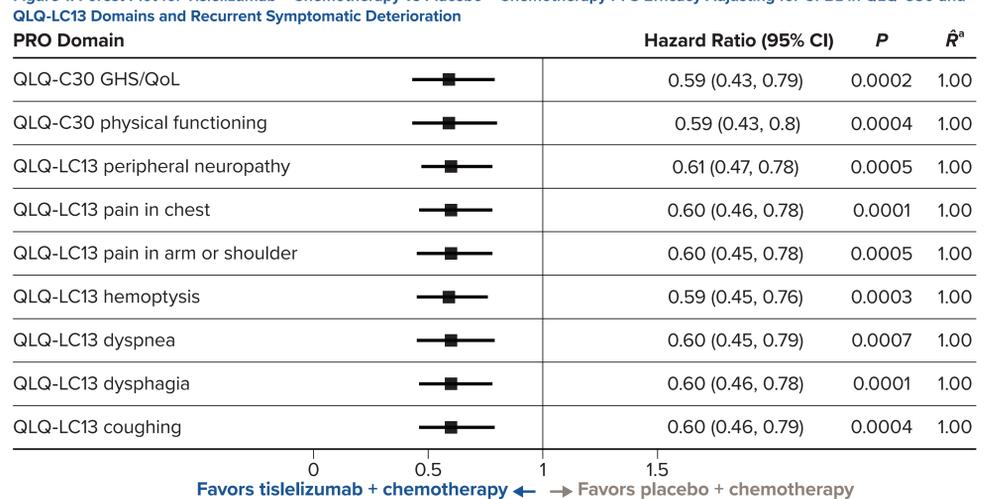
Table 2. Tislelizumab PFS Efficacy Adjusting for Change From Baseline in QLQ-C30 and QLQ-LC13 Domains and PRO Symptom Deterioration (Recurrent)

EORTC Domain	Parameter	P	\hat{R}^2	HR (95% CI)
QLQ-C30 GHS/QoL	Recurrent deterioration event-T+C treatment effect ^b	0.694	1.00	0.93 (0.634, 1.348)
	Recurrent deterioration event-longitudinal effect	<0.001	1.01	0.96 (0.948, 0.963)
	PFS event-recurrent deterioration event (frailty)	0.155	1.02	14.0 (0.155, 223.65) ^c
QLQ-C30 physical functioning	Recurrent deterioration event-T+C treatment effect ^b	0.658	1.00	0.92 (0.648, 1.308)
	Recurrent deterioration event-longitudinal effect	<0.001	1.01	0.99 (0.978, 0.991)
	PFS event-recurrent deterioration event (frailty)	0.018	1.02	26.4 (4.011, 287.76) ^c
QLQ-LC13 coughing	Recurrent deterioration event-T+C treatment effect ^b	0.259	1.01	0.63 (0.267, 1.410)
	Recurrent deterioration event-longitudinal effect	<0.001	1.04	1.12 (1.097, 1.153)
	PFS event-recurrent deterioration event (frailty)	0.431	1.01	3.60 (0.045, 73.6) ^c
QLQ-LC13 dysphagia	Recurrent deterioration event-T+C treatment effect ^b	0.677	1.00	1.25 (0.422, 3.741)
	Recurrent deterioration event-longitudinal effect	<0.001	1.01	1.30 (1.225, 1.392)
	PFS event-recurrent deterioration event (frailty)	0.441	1.01	0.36 (0.017, 22.4) ^c
QLQ-LC13 dyspnea	Recurrent deterioration event-T+C treatment effect ^b	0.936	1.00	1.02 (0.609, 1.723)
	Recurrent deterioration event-longitudinal effect	<0.001	1.00	1.14 (1.113, 1.163)
	PFS event-recurrent deterioration event (frailty)	0.167	1.01	7.62 (0.138, 108.75) ^c
QLQ-LC13 hemoptysis	Recurrent deterioration event-T+C treatment effect ^b	0.317	1.01	0.54 (0.158, 1.754)
	Recurrent deterioration event-longitudinal effect	<0.001	1.35	1.67 (1.457, 1.925)
	PFS event-recurrent deterioration event (frailty)	0.767	1.01	1.51 (0.021, 58.71) ^c
QLQ-LC13 pain in arm or shoulder	Recurrent deterioration event-T+C treatment effect ^b	0.064	1.00	0.51 (0.256, 1.040)
	Recurrent deterioration event-longitudinal effect	<0.001	1.00	1.13 (1.104, 1.159)
	PFS event-recurrent deterioration event (frailty)	0.330	1.05	3.78 (0.065, 67.56) ^c
QLQ-LC13 chest pain	Recurrent deterioration event-T+C treatment effect ^b	0.593	1.00	0.83 (0.421, 1.631)
	Recurrent deterioration event-longitudinal effect	<0.001	1.01	1.13 (1.102, 1.156)
	PFS event-recurrent deterioration event (frailty)	0.429	1.00	3.43 (0.042, 77.93) ^c
QLQ-LC13 peripheral neuropathy	Recurrent deterioration event-T+C treatment effect ^b	0.163	1.01	0.59 (0.282, 1.226)
	Recurrent deterioration event-longitudinal effect	<0.001	1.12	1.22 (1.169, 1.282)
	PFS event-recurrent deterioration event (frailty)	0.647	1.00	2.38 (0.024, 89.19) ^c

Notes: Each model was adjusted for the following stratification factors: age (<65 years vs ≥ 65 years of age), geographic region (China vs non-China), refractory status (yes vs no), del(17p)/TP53 mutation status (present vs absent), cancer type (CLL vs SLL), and baseline PRO measurement (in the linear mixed models). Significant effects are highlighted in blue. Markov chain trace and density plots were also used to characterize quality of model convergence. An \hat{R}^2 statistic with a value of 1.2 indicated acceptable convergence. ^aTreatment effect was coded as tislelizumab versus placebo with the former as the effect group. ^bAssociation parameter and not HR. ^cAbbreviations: Δ_{BL} , change from baseline; CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; GHS/QoL, global health status/quality of life; HR, hazard ratio; PRO, patient-reported outcome; QLQ-C30, Quality of Life Questionnaire – Core 30; QLQ-LC13, Quality of Life Questionnaire – lung cancer module.

- The PFS benefit with tislelizumab + chemotherapy remained robust after substantial adjustment beyond only stratification factors: PFS HRs after adjusting for GHS/QoL, physical functioning, and ES-SCLC-specific symptoms (HR: 0.59-0.61; $P<0.001$), corresponding to a 39-41% lower risk of progression events (disease progression/death) versus placebo + chemotherapy (Figure 1)

Figure 1. Forest Plot for Tislelizumab + Chemotherapy vs Placebo + Chemotherapy PFS Efficacy Adjusting for CFBL in QLQ-C30 and QLQ-LC13 Domains and Recurrent Symptomatic Deterioration



Notes: Markov chain trace and density plots were also used to characterize quality of model convergence. An \hat{R}^2 statistic with a value of near 1.2 indicated acceptable convergence. ^aAbbreviations: CI, confidence interval; CFBL, change from baseline; GHS/QoL, global health status/quality of life; HR, hazard ratio; PRO, patient-reported outcome; QLQ-C30, Quality of Life Questionnaire – Core 30; QLQ-LC13, Quality of Life Questionnaire – lung cancer module.

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DISCLOSURES

DH has declared no conflicts of interest. BB, TQ, CC, GB, and TV are employees of BeOne Medicines, Ltd.

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