Longitudinal Associations Between Patient-Reported Symptomatic Dyspnea Deterioration and Investigator-Reported Event-Free Survival in Resectable Non-Small Cell Lung Cancer: Results From the RATIONALE-315 Trial

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INTRODUCTION

- The RATIONALE-315 study (NCT04379635) compared the efficacy and safety of neoadjuvant tislelizumab (anti-PD-1) plus chemotherapy and adjuvant tislelizumab versus placebo plus chemotherapy in patients with resectable stage II or IIIA non-small cell lung cancer (NSCLC)[1]
- Interim analysis data demonstrated that neoadjuvant tislelizumab plus chemotherapy with adjuvant tislelizumab demonstrated a clinically meaningful and statistically significant benefit for event-free-survival (EFS) (HR [95% CI], 0.56 [0.40-0.79]; 1-sided *P*=.0003), while also maintaining or improving patient-reported outcomes (PROs)[1,2]
- Among PROs, dyspnea is one of the most commonly reported and clinically relevant symptoms in NSCLC, and has been previously identified as an independent predictor of survival[3,4]
- Given its prognostic value, the current analyses aimed to examine the association between longitudinal change in dyspnea scores, patient-reported dyspnea symptom deterioration events, and masked independent central review-assessed EFS

METHODS

Study Design and Patients

- These analyses were conducted using RATIONALE-315 trial data
  - Eligible patients were randomized (1:1) to either 3-4 cycles of neoadjuvant tislelizumab 200 mg or placebo (IV every 3 weeks) plus chemotherapy, then surgery and up to eight cycles of adjuvant tislelizumab 400 mg or placebo (IV every 6 weeks)

Measures

- The PRO-based dyspnea symptom deterioration endpoint was assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-LC13, a lung cancer–specific module designed to capture symptoms most prevalent to patients with NSCLC[5]
- Investigator-reported EFS was analyzed as the time-to-event (TTE) endpoint
- PRO dyspnea deterioration score was defined using threshold of change ≥10 increase from baseline,[6] confirmed by at least one consecutive worsening cycle

Statistical Analyses

- All randomized patients in the intent-to-treat (ITT) population who completed the baseline and ≥1 postbaseline QLQ-LC13 assessment were eligible
- Treatment efficacy for the dyspnea symptom endpoint was analyzed via incorporation of a linear mixed model for longitudinal change from baseline in dyspnea scores and a cox proportional hazard model for recurrent dyspnea symptom deterioration events, and TTE analysis
  - The treatment effect was coded as neoadjuvant tislelizumab versus neoadjuvant placebo with perioperative tislelizumab with neoadjuvant platinum-based chemotherapy as the effect group
- All analyses were adjusted for the following factors: tislelizumab (vs placebo), study day (treated as continuous), squamous (histology, squamous vs nonsquamous), stage II (vs stage IIIA), PD-L1 expression >1% (vs <1%/not evaluable), baseline score, and an interaction between tislelizumab and study day
- Multiple comparison issues were addressed using the method of Benjamini and Yekutieli (2001) for parameters of interest[7]
- 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 date of August 21, 2023, the ITT population consisted of a total of 453 patients randomized to receive tislelizumab (N=226) or placebo (N=227)
  - Patient demographics and baseline disease characteristics were generally balanced across the arms and have been reported elsewhere[1] (**Table 1**)
- The analytic sample for these analyses included a total of N=419 patients who completed the QLQ-LC13 (tislelizumab, n=211 [50.36%]; placebo, n=208 [49.64%])

Table 1. Patient Demographic and Clinical Characteristics

	Tislelizumab (N=226)	Placebo (N=227)
Median age (IQR), years	62.0 (57-67)	63.0 (56-68)
<65, n (%)	143 (63)	129 (57)
≥65, n (%)	83 (37)	98 (43)
Sex, n (%)		
Male	205 (91)	205 (90)
Female	21 (9)	22 (10)
ECOG performance status, n (%)		
0	142 (63)	154 (68)
1	83 (37)	73 (32)
Missing	1 (<1)	0
Smoking status, n (%)		
Current	43 (19)	52 (23)
Former	150 (66)	138 (61)
Never	33 (15)	37 (16)
Disease stage, n (%)[a]		
II	92 (41)	91 (40)
IIIA	132 (58)	133 (59)
Histology, n (%)		
Squamous	179 (79)	175 (77)
Nonsquamous	45 (20)	50 (22)
Other[b]	2 (1)	2 (1)

[a]Disease stage IB (tislelizumab arm, n=1; placebo arm, n=0); stage IIIB (tislelizumab arm, n=1; placebo arm, n=3). The patient with stage IB disease and the four patients with stage IIIB disease were incorrectly enrolled into the study.
[b]As reported on the case report form; patients with mixed histology were categorized as "other."
Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

Longitudinal Analysis Evidence

- Results from the longitudinal analysis, which adjusted for baseline dyspnea scores suggested that patients treated with tislelizumab had slightly higher average dyspnea scores; however, this difference was not statistically significant (estimate: 2.28; 95% CI: 0.41, 4.17; adjusted *P*=0.0829) (**Table 2**)
- Patients with higher baseline dyspnea scores (worse symtoms) were more likely to experience greater reductions in dyspnea scores over time, indicating that baseline dyspnea was a strong predictor of longitudinal symptom trajectory (estimate: −0.67; *P*<0.0001) (**Table 2**)
- The interaction between tislelizumab and study day (tislelizumab × day) was statistically significant after multiplicity adjustment (estimate: −0.01; 95% CI: −0.02, 0.00; unadjusted *P*=0.0010; [adjusted]=0.0094), suggesting a protective effect over time in mitigating worsening dyspnea symptoms (**Table 2**)

Table 2. Treatment Effect of Tislelizumab on Longitudinal Change in Patient-Reported Dyspnea Symptoms

Parameter	Estimate (95% CI)	*P*	$\widehat{R}$[a]	*P* (Adjusted)
(Intercept)	11.01 (8.64, 13.40)	0.0000	1.0061	–
Tislelizumab[b]	2.28 (0.41, 4.17)	0.0183	1.0034	0.0829
Study day	0.00 (0.00, 0.01)	0.7241	1.0646	–
Squamous	−1.24 (−3.21, 0.71)	0.2120	1.0018	–
Stage II	0.63 (−1.04, 2.34)	0.4641	1.0177	–
PD-L1 expression ≥1%	0.08 (−1.57, 1.73)	0.9238	1.0012	–
Baseline	−0.67 (−0.74, −0.61)	0.0000	1.0077	–
Tislelizumab × day	−0.01 (−0.02, 0.00)	0.0010	1.0047	**0.0094**
σ	9.62 (9.32, 9.94)	0.0000	1.0595	–

Bold font means statistically significant.
[a]A statistic with a value of 1.0 indicated acceptable convergence.
[b]Treatment effect was coded as tislelizumab + chemotherapy versus placebo + chemotherapy with the former as the effect group.
Abbreviations: CI, confidence internal; PD-L1, programmed death ligand 1; $\widehat{R}$, Gelman-Rubin convergence diagnostic; σ, sigma.

Time-to-Event Analysis Evidence

- In the recurrent event component, a statistically significant association (HR=1.06; 95% CI: 1.04-1.09; *P*<0.0001) was observed for dyspnea score change, indicating that each 1-point worsening in dyspnea score over time was associated with a 6% increased risk of experiencing a recurrent dyspnea deterioration event (**Table 3**)
- In the terminal event component, tislelizumab + chemotherapy demonstrated a 54% reduction in the risk of experiencing a terminal event (thus a higher chance of EFS) compared to placebo (HR=0.46; 95% CI: 0.23-0.79; *P*=0.0044) (**Table 3**)
  - Patients with stage II disease had a statistically significant 41% lower risk of experiencing an investigator-assessed event compared to those with stage III disease (HR=0.59; 95% CI: 0.33-0.94; *P*=0.0255)

Table 3. Time-to-Event Outcomes for Dyspnea Deterioration and IREFS (Terminal Event)

Parameter	Estimate (95% CI)	*P*	$\widehat{R}$[a]	*P* (Adjusted)	HR (95% CI)
Strata: Recurrent					
Tislelizumab	−0.01 (−0.40, 0.39)	0.9748	1.0060	1.0000	0.99 (0.67, 1.47)
Squamous	0.02 (−0.23, 0.28)	0.8911	1.0055	–	1.02 (0.79, 1.32)
Stage II	−0.09 (−0.32, 0.14)	0.4397	1.0143	–	0.91 (0.73, 1.15)
PD-L1 expression >1%	−0.11 (−0.33, 0.12)	0.3593	1.0039	–	0.90 (0.72, 1.13)
Dyspnea change	0.06 (0.04, 0.09)	<0.0001	1.4963	**<0.0001**	1.06 (1.04, 1.09)
Strata: Terminal					
Tislelizumab[b]	−0.79 (−1.49, −0.23)	0.0044	1.0410	**0.0266**	0.46 (0.23, 0.79)
Squamous	−0.13 (−0.69, 0.44)	0.6124	1.0187	–	0.88 (0.50, 1.55)
Stage II	−0.53 (−1.12, −0.06)	0.0255	1.0194	–	0.59 (0.33, 0.94)
PD-L1 expression ≥1%	−0.19 (−0.72, 0.26)	0.4462	1.0140	–	0.83 (0.49, 1.30)
Dyspnea change	−0.01 (−0.03, 0.02)	0.6072	1.0155	1.0000	0.99 (0.97, 1.02)
Frailty	3.81 (−1.64, 7.30)	0.1495	1.1213	0.5426	44.96 (0.19, 1486.56)[c]

Bold font means statistically significant.
[a]A statistic with a value of 1.0 indicated acceptable convergence.
[b]Treatment effect was coded as tislelizumab + chemotherapy versus placebo + chemotherapy with the former as the effect group.
[c]Association parameter and not an HR.
Abbreviations: CI, confidence interval; HR, hazard ratio; IREFS, investigator-reported event-free survival; PD-L1, programmed death ligand; $\widehat{R}$, Gelman-Rubin convergence diagnostic.

CONCLUSIONS

- Compared to placebo + chemotherapy, tislelizumab + chemotherapy demonstrated a statistically significant time-dependent protective effect (ie, experienced less worsening) on patient-reported dyspnea symptoms over the course of the study
- Worsening in patient-reported dyspnea symptoms was significantly associated with an increased risk of future dyspnea deterioration events (ie, recurrent symptomatic deterioration events), highlighting its potential utility as an early, patient-centered indicator of clinical decline that may inform timely clinician intervention
- Tislelizumab + chemotherapy significantly reduced the hazard of a terminal event (ie, an EFS event) by 54% compared to placebo + chemotherapy
- These analyses suggest that patient-reported disease-specific symptoms, such as dyspnea, may enhance clinical decision-making while informing endpoint selection in future oncology clinical trials among patients with resectable NSCLC

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DISCLOSURES

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